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THE CENTRAL PATH OF THE PUPILLOCONSTRICTOR REFLEX IN RESPONSE TO LIGHT

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A part of the work being done on the optic system in the laboratory of Northwestern University Medical School has been concerned with determining the central path of the pupilloconstrictor reflex in response to light. Information concerning this path should be of general interest as well as of clinical value in providing the anatomic basis for an understanding of the Argyll Robertson pupil and other disturbances of pupillary innervation.

Certain features of the course taken by the light reflex are already known. The work of Karplus and Kreidl [1] on the cat and the monkey established that the constrictor pathway runs centrad from the optic tract in the brachium of the superior colliculus. In spite of a large amount of contrary evidence, the view has long been held that the impulses pass from the brachium into the tectum of the superior colliculus, and thence by way of the tectobulbar tract to the sphincter nucleus of the oculomotor nerve.

In opposition to this, the constrictor reflex to light was found to remain intact after extirpation of the tectum of the superior colliculus, by Knoll [2] in the rabbit, Bechterew [3] in the dog, Ferrier and Turner [4] in the monkey, Levinsohn in the rabbit [5] and in the monkey,[6] Bern-

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1. Karplus, J. P., and Kreidl, A.: Ueber die Bahn des Pupillarreflexes, Arch. f. d. ges. Physiol. **149**:115, 1913.

2. Knoll, P.: Beiträge zur Physiologie der Vierhügel, Beitr. z. Anat. u. Physiol. **4**:109, 1869.

3. Bechterew, W.: Ueber den Verlauf der die Pupille verengenden Nervenfasern im Gehirn und über die Localisation eines Centrum für die Iris und Contraction der Augenmuskeln, Arch. f. d. des. Physiol. **31**:60, 1883.

4. Ferrier, D., and Turner, W. A.: Experimental Lesions of the Corpora Quadrigemina in Monkeys, Brain **24**:27, 1901.

5. Levinsohn, G.: Beiträge zur Physiologie des Pupillarreflexes, Arch. f. Ophth. **59**:191 and 436, 1904.

6. Levinsohn, G.: Experimentelle Untersuchungen über die Beziehungen des vorderen Vierhügels zum Pupillarreflex, Arch. f. Ophth. **72**:367, 1909.

heimer [7] in the monkey and Keller and Stewart [8] in the cat. Spiegel and Nagasaka [9] found that destruction of the medial part of the tectum and the central gray matter did not destroy the light reflex.

With the tectum thus excluded, the question remains as to the path of the constrictor impulse from the brachium of the superior colliculus to the sphincter nucleus of the oculomotor. The answer to the question is given in this paper, which reports the results obtained from a systematic stimulation of the interior of the caudal part of the diencephalon and the rostral half of the midbrain in normal cats. While the general course of the light reflex pathway has been determined, we are not yet able to say where the synapse or synapses which almost certainly occur in this pathway are situated.

METHOD

All the data reported here were obtained from stimulation of the brains of normal cats. For this purpose the Horsley-Clarke apparatus was utilized. The instrument and its manner of use have been described by Ingram, Ranson, Hannett, Zeiss and Terwilliger.[10] It may be mentioned briefly here as an apparatus, accurately adjustable to the cat's head, which enables a bipolar needle electrode to be oriented in the interior of the brain by readings along the anteroposterior, mediolateral and dorsoventral scales of the instrument.

The bipolar needle electrode consisted of two lengths of nichrome wire insulated and cemented together with baked enamel. Its diameter through the widest axis was 0.8 mm. and the shortest distance between the exposed tips was 0.2 mm. The current was supplied by a single dry cell registering 1.5 amperes attached to a Harvard inductorium, the secondary coil of which was set at 9 cm.

The animals were under a light anesthesia of pentobarbital sodium, from 14 to 18 mg. per kilogram of body weight. If more anesthestic was necessary to prevent struggling, supplemental ether was added by means of a tracheal cannula and ether bottle. After the skin had been incised, the temporal muscles were reflected and about a square inch of the calvarium was removed. In many of the cats the superior sagittal sinus was tied off and the dura removed.

The instrument was then adjusted to the [illegible]al's head and stimulation was begun laterally on the left side of the brain and extended to the midline and onto the right side. The electrode was inserted into the brain at a point 10 mm. from the midline, in a plane 7 or 8 mm. in front of the zero point of the instrument. After stimuli had been applied, the electrode was removed and reinserted 1 mm. nearer the midline. Ten or more such punctures were made in one transverse

7. Bernheimer, S.: Weitere experimentelle Studien zur Kenntnis der Lage des Sphinkter-und Levatorkerns, Arch. f. Ophth. **70**:539, 1909.

8. Keller, A. D., and Stewart, L.: The Superior Colliculus and the Pupillary Light Reflex in the Cat, Am. J. Physiol. **101**:64, 1932.

9. Spiegel, E. A., and Nagasaka, G.: Experimentelle Studien am Nerven-System: VI. Ueber die Beziehung des Pupillenreflexbogens zum vordern Vierhügel, Arch. f. d. ges. Physiol. **215**:120, 1927.

10. Ingram, W. R.; Ranson, S. W.; Hannett, F. I.; Zeiss, F. R., and Terwilliger, E. H.: Results of Stimulation of the Tegmentum with the Horsley-Clarke Stereotaxic Apparatus, Arch. Neurol. & Psychiat. **28**:513 (Sept.) 1932.

plane, with millimeter intervals between punctures; then the electrode was moved 2 mm. caudally and another similar transverse row of punctures completed. Four or five such rows were usually completed in each brain. Stimulation was made at millimeter intervals along each of these punctures as the needle was inserted vertically through the brain. The coordinates of each point stimulated, together with the reactions observed, were recorded in systematic notes and later correlated with microscopic sections of the brain.

In this way the caudal half of the diencephalon, the superior colliculus and the dorsal part of the mesencephalic tegmentum were systematically explored in each of twelve cats. As a check, stimulation was begun in the caudal portion of the superior colliculus and extended rostrally into the diencephalon in each of three cats. In another set of six cats, the constrictor response was picked up in the optic tract ventral to the lateral geniculate body and was followed mediad in the brain stem, with millimeter intervals between punctures. In the latter set it was endeavored to keep on the trail only of the constrictor response; no attempt was made to explore the surrounding parts of the brain.

At the conclusion of each experiment, and before removal of the stereotaxic instrument, four wires were inserted in the brain; these marked off the explored area and served as guides in cutting out the block for microscopic study, making it possible to cut the sections in the same planes as those occupied by the punctures. Formaldehyde was injected into the head, and the brain was removed, trimmed and prepared by the Weil method.

The rows of punctures were identified in the sections, the punctures appearing as fine vertical tracts of hemorrhage. The level of section was identified and the punctures were plotted on a standard series of drawings. The shrinkage of the brain due to fixation and embedding was calculated and allowed for in each instance, and the location of the stimulated points was determined by measuring up from the base of each puncture. These locations could be checked by comparison with the position of points which had been definitely marked by stopping certain of the punctures when an especially strong reaction was obtained. Such points could be readily identified at the ends of the punctures. All the points stimulated were plotted on the drawings and their reactions indicated with appropriate symbols. In this way ninety-three drawings of cross-sections of the brain were prepared on which the locations of all the points stimulated, together with the reactions obtained, were indicated. The arrangement of the large amount of data in this way made for easy study, correlation and reference.

OBSERVATIONS

Optic Tract.—The most rostral stimuli were situated at the caudal border of the optic chiasm. The optic tract from this level centrad was thoroughly explored, and always yielded marked bilateral constriction on stimulation. The pupillary dilatation obtained by Karplus and Kreidl [1] from the part of the optic tract which underlies the hypothalamus must have been due to the escape of current, as was, indeed, suspected by them. No constrictor responses were ever obtained from stimulation of the region of the internal capsule or of the cerebral peduncle, except when the oculomotor nerve was involved. It is therefore impossible to consider the light reflex path as being mediated by

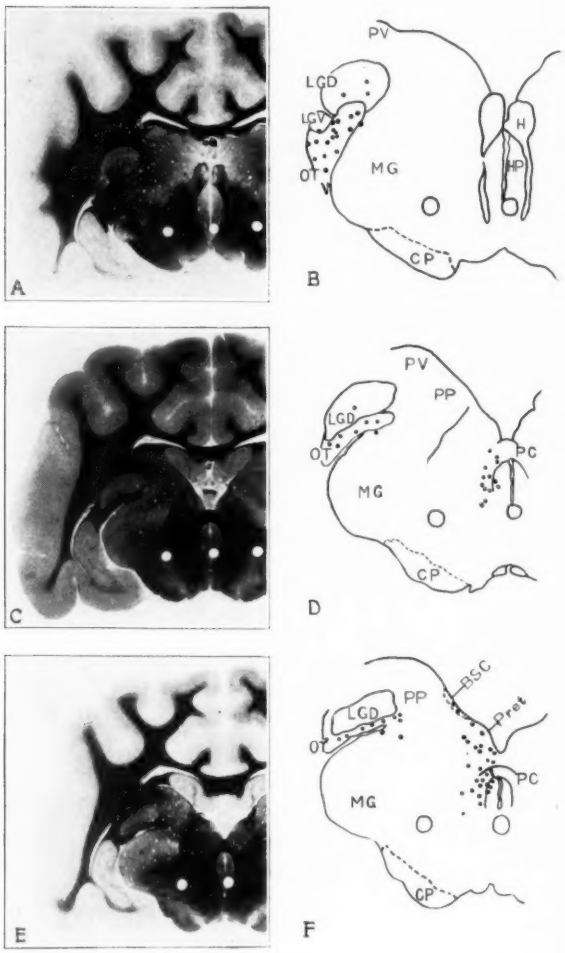

Fig. 1.—*A*, *C* and *E* are enlarged photographs of frontal sections through the cat's brain stained by Weil's method. *A* is at the level of the middle of the lateral geniculate body. *C* and *E* represent sections through the lateral geniculate body and posterior commissure and are situated respectively 1.1 mm. and 1.8 mm. behind the level of *A*. *B*, *D* and *F* are outline drawings from the same levels. The black dots represent the points from which pupillary constriction was elicited. The abbreviations indicate: *BSC*, brachium of superior colliculus; *CP*, cerebral peduncle (basis); *H*, habenula; *HP*, habenulopeduncular tract; *LGD*, lateral geniculate body (dorsal part); *LGV*, lateral geniculate body (ventral part); *MG*, medial geniculate body; *OT*, optic tract; *Pret*, pretectal area; *PC*, posterior commissure; *PP*, pulvinar posterior; *PV*, pulvinar.

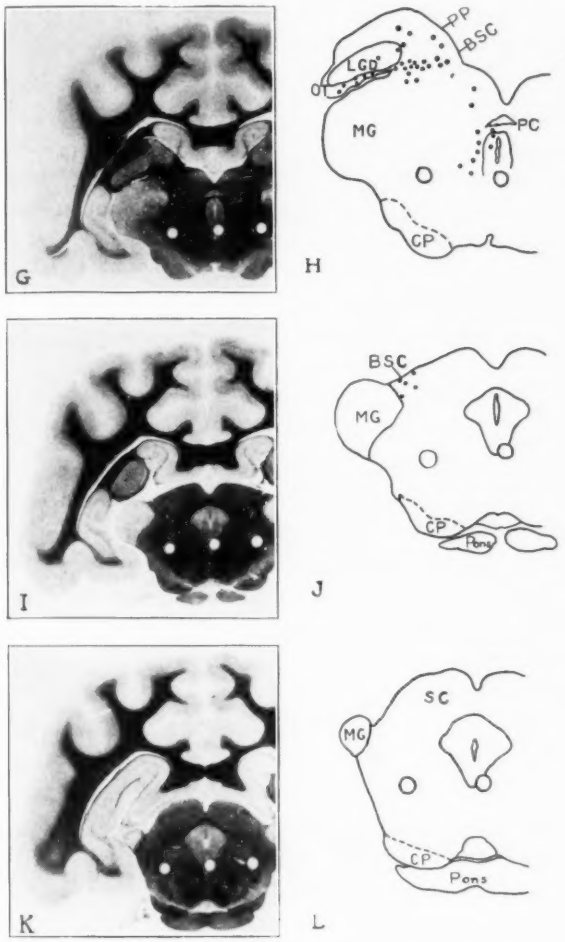

Fig. 2.—*G*, *I* and *K* are enlarged photographs of frontal sections of the cat's brain stained by Weil's method. *G* is at the level of the caudal end of the lateral geniculate body, 0.4 mm. behind the level represented in figure 1 *E*. *I* and *K* represent sections through the superior colliculus, 0.9 and 1.6 mm., respectively, behind the level of *G*.

H, *J* and *L* are outline drawings from the same levels. The black dots represent the points from which pupillary constriction was elicited. It will be noticed that the pupillary constrictor path runs dorsad and mediad in the optic tract (fig. 1 *B*, *D* and *F*) thence mediad in the superior quadrigeminal brachium (fig. 2 *H*) and pretectal area (fig. 1 *F*) to the region of the posterior commissure (figs. 1 *D* and *F* and 2 *H*). It is apparent that some pupilloconstrictor fibers run some distance backward in the brachium and then turn forward again (fig. 2 *J*). The abbreviations indicate: *BSC*, brachium of superior colliculus; *CP*, cerebral peduncle (basis); *LGD*, lateral geniculate body (dorsal part); *MG*, medial geniculate body; *OT*, optic tract; *PC*, posterior commissure; *Pons*, pons; *PP*, pulvinar posterior; *SC*, superior colliculus.

either the anterior or the posterior accessory optic tract, since these tracts run around or through the basis pedunculi.

Region of the Lateral Geniculate Body.—The constrictor responses obtained from stimulation of the optic tract peripheralward of the lateral geniculate body represent stimulation of the light reflex path from the retina. From the region of the lateral geniculate body centrad, however, there is always the possibility that stimulation is activating not the light reflex path alone, but also efferent fibers from a cortical constrictor center. For this reason, until the two are differentiated caution must be exercised in interpreting the results. However, it seems certain that the light reflex pathway is contained within the responsive regions.

Bilateral constriction was obtained from stimulation of the optic tract ventral to the lateral geniculate body (figs. 1 *A* to *F*; 2 *G* and *H*). Not all the responses were elicited from the optic tract, however. A few marked and many weak reactions came from points near the dorsal or ventral surface of the tract in the lateral or medial geniculate body. These seem most probably to represent a spread of current to fibers in the optic tract.

Brachium of the Superior Colliculus.—Marked bilateral constrictor responses were obtained by stimulating the brachium of the superior colliculus and the gray matter between the optic tract and the brachium slightly rostral to the level at which the two become continuous (figs. 1 *E* and *F*; 2 *G* to *J*). The distance involved is so short that these responses from the gray matter can probably best be considered as being due to a spread of the current to the optic tract laterally, to the brachium medially or to the transition from one to the other caudally.

Superior Colliculus.—A thorough exploration of the tectum of the superior colliculus failed to elicit constrictor responses from it anywhere except in the immediate neighborhood of the brachium (fig. 2 *I* to *L*). Many workers have observed a dilatation of the pupils to result from stimulation of the superior colliculus (Knoll,[2] Ferrier,[11] Karplus and Kreidl[1]). Our results indicate that dilatation of the pupil is not obtained until the electrode passes through the tectum and reaches the dorsal border of the tegmentum or central gray matter. Localized stimulation of the tectum is uniformly devoid of any apparent result. Certainly it never produces a constriction of the pupil. The negative results from stimulation, together with the experiments in extirpation previously mentioned, clearly point to the fact that the constrictor impulses do not pass from the anterior quadrigeminal brachium to the

11. Ferrier, D.: The Functions of the Brain, ed. 2, London, Smith, Elder & Co., 1886.

oculomotor nucleus by way of the superior colliculus. Our experiments indicate that the gap is bridged rostral to the superior colliculus, in the pretectal region, with a partial decussation in the posterior commissure. It is true that tumors of the corpora quadrigemina have been known to cause Argyll Robertson pupils (Wilson,[12] Wilson and Gerstle[13]), but these may have exerted pressure on the posterior commissure and other structures in the neighborhood.

Pretectal Region.—Bilateral constrictor responses were obtained from stimulation of the pretectal region at the level shown in figures 1 *E* and *F*. A comparison of this level with that of figure 2 *G* and *H* shows that these responses are a rostromedial continuation of the constrictor responses obtained from the brachium of the superior colliculus. Only a small number of responses were obtained from the pretectal area, and it is apparent that further work is needed on this region.

The pretectal region may be regarded as a zone of transition between the thalamus and tectum. It contains, in addition to the pretectal nucleus, a compact group of cells which has been called the nucleus of the optic tract. There is reason to believe that optic nerve fibers end in both of these nuclei. But although constrictor responses have been obtained from these nuclei, we are unable to say whether or not the path is interrupted by synapses within them.

Posterior Commissure.—One of the clearest features of this series of experiments is the fact that marked constrictor responses could be elicited with the greatest regularity by stimulation of the posterior commissure and the fibers emerging from it and running ventrocaudad around the central gray matter to the rostral end of the oculomotor nucleus (fig. 1 *C* to *F*—2 *G* and *H*). We have no hesitation in saying, on the basis of the great excitability exhibited by this system and the negative results from other parts, that the posterior commissure and the fibers issuing from it and arching around the rostral end of the central gray matter constitute an important part of the pupilloconstrictor pathway.

Bilateral constrictor responses, approximately equal in the two eyes, were obtained from stimulation of the posterior commissure and the region immediately dorsal and lateral to it. Stimulation of the commissural fibers as they curve ventrocaudad around the central gray matter at the level where the aqueduct opens into the third ventricle yielded as a rule a marked ipsilateral and a weak contralateral constriction. Stimulation of the root fibers of the oculomotor nerve within

12. Wilson, S. A. K.: Some Problems in Neurology: I. The Argyll-Robertson Pupil, J. Neurol. & Psychopath. **2**:1, 1921.

13. Wilson, S. A. K., and Gerstle, M.: The Argyll-Robertson Sign in Mesencephalic Tumors, Arch. Neurol. & Psychiat. **22**:9 (July) 1929.

the tegmentum caused ipsilateral constriction, usually accompanied by contralateral dilatation.

Since a bilateral constrictor response, approximately equal in both eyes, obtained dorsolateral to the posterior commissure gives way to what is in the main an ipsilateral constriction ventral to the commissure, it would appear that a certain proportion of the constrictor impulses cross in that commissure. The fact that a weak contralateral constriction is usually obtained from stimulation in the region through which the fibers of the posterior commissure run ventrad and caudad around the central gray matter indicates that a second, smaller crossing takes place ventral to the aqueduct. We are unable to say whether this is a crossing of secondary optic or of oculomotor fibers.

There is both clinical (Behr [14]) and experimental evidence which clearly indicates that the light reflex pathway undergoes a partial central crossing. Bernheimer [15] found that both the consensual and the direct constrictor reaction remained intact after midsagittal section of the optic chiasm in the monkey. The results of Karplus and Kreidl,[1] who obtained bilateral constriction from stimulation of one superior quadrigeminal brachium in the cat and in the monkey, show that a decussation is situated central to this tract. There is some evidence in the literature that this crossing takes place in the posterior commissure. Darkschewitsch [16] found an impairment of the light reflex after injury to the posterior commissure in rabbits, and drew the conclusion that the constrictor reflex path traveled over the posterior commissure. More recently, Lenz,[17] in human material stained by the Bielschowsky method, followed a fiber band from the brachium of the superior colliculus across the posterior commissure and down to the sphincter nucleus. He regarded this as the afferent limb of the light reflex arc. Reference should be made also to the work of Sachs,[18] who obtained bilateral constriction from stimulation of the posterior commissure in the monkey, and to that of Papez and Freeman [19] who, after a lesion lateral to the posterior commissure in the rat, traced degeneration across the commissure and down to the ciliary nucleus.

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14. Behr, C.: Die Lehre von den Pupillenbewegungen, Berlin, Julius Springer, 1924.

15. Bernheimer, S.: Die Reflexbahn der Pupillarreaction, Arch. f. Ophth. **47**:1, 1898.

16. Darkschewitsch, L.: Versuche über die Durchschneidung der hinteren Gehirncommissur beim Kaninchen, Arch. f. d. ges. Physiol. **38**:120, 1886.

17. Lenz, G.: Untersuchungen über die intrazerebrale Bahn des Pupillarreflexes, Ber. u. d. Versamml. d. deutsch. ophth. Gesellsch. **46**:140, 1927.

18. Sachs, E.: On the Structure and Functional Relations of the Optic Thalamus, Brain **32**:95, 1909.

19. Papez, J. W., and Freeman, G. D.: Superior Colliculi and Their Fiber Connections in the Rat, J. Comp. Neurol. **51**:409, 1930.

It is true that section of the posterior commissure does not abolish the light reflex. But the results of Harris [20] and of Karplus and Kreidl [1] cannot be brought as evidence against a partial decussation in that commissure.

A reexamination of the original records of mesencephalic stimulation carried out by Ingram, Ranson, Hannett, Zeiss and Terwilliger [10] shows that they obtained bilateral pupillary constriction from stimulation of the pretectal region and the nucleus of the posterior commissure, but not from stimulation of the superior colliculus or the fibers of the tectobulbar tract as they encircle the central gray matter. Similar results were reported by Ranson and Magoun [21] in a paper on respiratory and pupillary reactions induced by electrical stimulation of the hypothala-

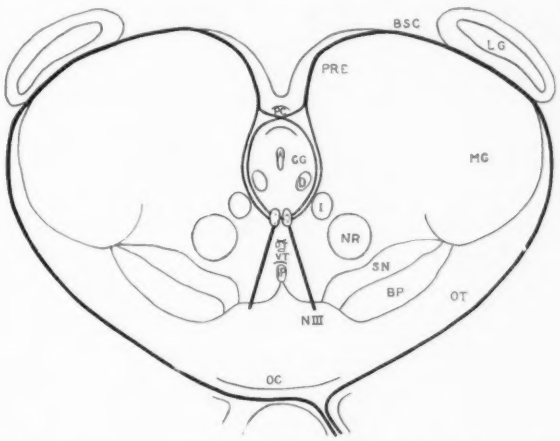

Fig. 3.—Diagram of the path for the pupillary light reflex. The location of the synapses are not indicated. The abbreviations indicate: *A*, aqueduct; *BSC*, brachium of superior colliculus; *BP*, basis pedunculi; *CG*, central gray matter; *D*, nucleus of Darkschewitsch; *DT*, dorsal tegmental decussation; *I*, interstitial nucleus; *IP*, interpeduncular nucleus; *LG*, lateral geniculate body; *MG*, medial geniculate body; *NR*, red nucleus; *NIII*, oculomotor nerve; *OC*, optic chiasm; *OT*, optic tract; *PC*, posterior commissure; *PRE*, pretectal area; *SN*, substantia nigra; *VT*, ventral tegmental decussation; *3*, oculomotor nucleus.

mus. It will be evident, therefore, that the mass of data on which our conclusions are based is greater than that furnished by the experiments reported in this paper.

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20. Harris, W.: Binocular and Stereoscopic Vision in Man and Other Vertebrates, with Special Reference to the Decussations of the Optic Nerves, the Ocular Movements and the Pupil Light Reflex, Brain **27**:107, 1904.

21. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933.

In order to mark definitely the points from which reactions were obtained in the dorsal part of the brain stem, many of the punctures were stopped at reactive points in the brachium, pretectal region and posterior commissure. For this reason the stimuli applied to the oculomotor nerve and its nucleus were few and have not been included in the drawings. While we see no reason to doubt that the Edinger-Westphal nucleus gives rise to the pupilloconstrictor fibers, a special investigation devoted to this question will be required before we can say what part of the oculomotor nucleus and which root bundles of the third nerve are concerned in the reaction.

SUMMARY

For convenience in summarizing our results, a diagram has been constructed (fig. 3). This diagram represents, simply in one plane, the localities in the brain stem from which constrictor responses are obtained from electrical stimulation. In the case of responses mediad to the lateral geniculate body, we cannot exclude the possible participation of efferent fibers from a constrictor region of the cortex. No evidence is presented as to the situation of intercalated neurons.

Constrictor responses are obtained from stimulation of the optic chiasm, the optic tract on the lateral surface of the brain stem and ventral to the lateral geniculate body, the brachium of the superior colliculus, the pretectal region, the posterior commissure, and the fibers emerging from it and arching ventrally around the central gray matter at the level of transition between the third ventricle and the cerebral aqueduct, and from the oculomotor nerve. The plan of decussation figured in the posterior commissure, with a second smaller and more ventrally placed crossing, seems the most satisfactory interpretation of the fact that marked bilateral constriction is obtained from stimulation of the posterior commissure and the region dorsolateral to it, while marked ipsilateral and weak contralateral constriction are obtained from stimulation of the fibers arching ventrally around the central gray matter.

Pupillary constriction was never obtained from stimulation of the superior colliculus.

DISCUSSION

Dr. Frederick Tilney, New York: This careful work of Dr. Ranson's makes it apparent that we need to revise our ideas concerning the termination of the light fibers in the optic system. We have all become accustomed to locating this termination in the superior colliculus. Now it appears that we must assume an entirely different location.

I do not see how there could be any possible doubt as to the facts produced by this careful method of exploration. It may, perhaps, be of interest—confirma-

tory, in a way, of the points which Dr. Ranson has just made—to cite some recent embryologic studies in several mammalian species which seem to lead to conclusions similar to Dr. Ranson's.

Among the fibers developed earliest in the brain are those which come from the lateral olfactory tract. A little later, the fibers of the optic system make their appearance in the form of a large bundle. This massive bundle runs up along the side of the diencephalon and ultimately sends a sizable extension backward on the side of the tectum. The entire bundle has the form of a scythe, the handle of which is formed by the long ascending fibers and the blade by the extension backward along the wall of the tectum mesencephali. Of the two parts in this optic system, the more constant is the handle of the scythe.

When I first began studying this region, I was inclined to believe that all the fibers ended in the tectum of the midbrain. In the early stages of development there is a tendency toward cortex formation in this area. Later studies convinced me that a large bundle of these optic fibers end in the pretectal region, a transitionary area between the diencephalon and the mesencephalon. Furthermore, I was able to trace long protoplasmic processes from this pretectal region to the posterior commissure and also to a smaller commissure lying ventrad to the gray matter below the aqueduct. This embryologic evidence seems to corroborate what Dr. Ranson has just demonstrated. From the standpoint of development it shows that some of the fibers, which apparently convey light impulses from the retina, terminate in the pretectal area, while some pass farther backward to enter the dorsal and ventral divisions of the posterior commissure.

Dr. E. A. Spiegel, Philadelphia: The painstaking experiments of Drs. Ranson and Magoun show that the rôle of the superior colliculus as a part of the pupillary reflex arc has been overestimated. They prove that part of the constrictor impulses reach the sphincter nucleus via the posterior commissure. The experiments on the posterior commissure are particularly interesting, as the pathogenesis of Argyll Robertson pupil was recently located here. Behr supposed that bilateral Argyll Robertson pupil is due to a lesion of the mesencephalic decussation of the pupillomotor fibers and that unilateral Argyll Robertson pupil is caused by a lesion between this decussation and the sphincter nucleus.

Recently Sven Ingvar assumed a marginal degeneration which in cases of unilateral Argyll Robertson pupil reaches the posterior commissure on the side of the immobilized pupil. The statement of Darkschevich, however, that destruction of this commissure causes a loss of the excitability of the oculomotor nerve has been refuted by Harris, Karplus and Kreidl. On the other hand, observations of Herrmann seem to corroborate Behr's theory, as he found lesions of the posterior commissure in a case of encephalitis, and in another of disseminated sclerosis, with Argyll Robertson pupil. It seemed, therefore, of some interest to study the light reflex of the pupil after experimental injuries to the posterior commissure. After severance of this bundle in cats in the midline as well as between the decussation and the sphincter nucleus, I observed a direct as well as a consensual pupillary reaction in both eyes. This does not conflict with the fact that part of the retinal impulses use the posterior commissure in order to reach the sphincter nucleus, as has been shown by the accurate stimulation experiments of Dr. Ranson. The pathogenesis of Argyll Robertson pupil, however, has to be sought outside this bundle.

Dr. W. G. Spiller, Philadelphia: I reported in *Brain*, in 1901, a case of complete defect of the visual system in a man 22 years of age. The orbits contained only a small amount of what appeared to be fibrous connective tissue,

but removal was not permitted. There were no optic foramina and no trace of the optic nerves, chiasm, optic tracts or external geniculate bodies. The superior colliculi were fully as large and as well developed as the inferior colliculi. These findings seemed to me to confirm von Monakow's opinion that the superior colliculi in man have a very subordinate rôle in vision. Von Monakow stated that it is certain that loss of both superior colliculi in man occasions very slight impairment of sight and leaves color vision intact.

Brouwer and Zeeman in their experimental work found that in monkeys the retina is also projected in the anterior corpora quadrigemina, but the bundles connected therewith are very small, especially on the uncrossed side. Secondary degenerations to this structure were absent in most of their cases. They also found that the number of degenerated fibers to the anterior corpora quadrigemina is smaller in monkeys than in cats. This finding seems to me to suggest that in the highest apes and especially in man the optic fibers to the superior colliculi are even less important, for it does not follow necessarily that conclusions regarding vision drawn from experiments on rabbits, cats and the lower apes are equally applicable to man.

In view of these conclusions regarding the representation of visual fibers in the superior colliculi, Ranson's findings regarding the so-called pupillary fibers are not surprising. Brouwer and Zeeman stated that it is usually accepted that the movements of the pupils are greatest when rays of light fall on the macular region, and they expected to find after macular lesions many degenerated fibers passing to the anterior corpora quadrigemina. The absence of such degenerated fibers led them to conclude that if the fibers for reflex movements of the pupil take origin in the macula they cannot be myelinated.

Dr. S. W. Ranson, Chicago: The embryologic course of the optic fibers, as outlined by Dr. Tilney, fits in very well with what we have found experimentally by stimulation of the optic pathways. It also fits in with certain observations made on adults by Lenz. Lenz was able to trace fibers from the superior quadrigeminal brachium through the pretectal region across the posterior commissure and down toward the oculomotor nucleus on the opposite side.

I think it is certainly true, as Dr. Spiegel has said, that section of the posterior commissure will not abolish the light reflex. We have not tried that ourselves, but observations in the literature point in that direction. This does not militate against the idea which we have in mind, since the crossing in the posterior commissure is obviously only partial, as shown in the diagram, and since there is also a secondary crossing ventral to the central gray matter.

Dr. Spiller's case of congenital absence of the eyes with fully developed superior colliculi serves to emphasize the fact that these bodies have many other connections besides those with the optic tract. In the lowest vertebrates nearly all of the fibers of the optic tract terminate in the midbrain and only a few fibers go to the thalamus. As one proceeds up the scale the number of fibers to the diencephalon increases, and with the evolution of the cerebral cortex the lateral geniculate body develops and becomes the chief end-station of the optic tract. In man, relatively few fibers go to the superior colliculi, and it is certain that these are not concerned either with vision or with the pupillary light reflex. The reference to the work of Brouwer and Zeeman is of special interest. Their failure to find macular fibers going to the anterior colliculi, although macular fibers play an important part in the pupillary light reflex, fits in well with our conception of the pathway for this reflex.

ELECTRICAL EXCITABILITY AND CYTO-ARCHITECTURE OF THE PREMOTOR CORTEX IN MONKEYS

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Recent experimental and clinical studies [1] on the "premotor area," i. e., the region of the cerebral cortex just anterior to the classic "motor area," indicate that this region is intimately concerned with motor activity and that it probably gives rise to important motor projection systems. As statements in the literature concerning the electrical excitability of this area lack precision and, indeed, are often conflicting, it has seemed desirable to carry out a carefully controlled analysis of the response of this region to faradic stimulation, before and after the removal of the motor area, and to correlate the results with detailed microscopic examination of the cortex. The present paper embraces the results of such a study.

The terms "motor" and "premotor" areas have been used throughout as synonymous, respectively, with "area 4" and "area 6" of Brodmann.

CONSIDERATIONS OF STRUCTURE

Area 4 of Brodmann (the motor cortex, area gigantopyramidalis of some authors, area FA of von Economo and Koskinas [2]) occupies, in the monkey (Pithecus [Macacus] rhesus of Elliot), the anterior wall of the central sulcus and about 5 to 7 mm. of the convexity of the precentral gyrus (fig. 4). This area occupies a relatively much greater portion of the precentral gyrus than it does in man. Microscopically, area 4 is one of the thickest portions of the cerebral cortex and is composed essentially of five layers, layer 4 (the internal granular) being practically absent. The chief microscopic peculiarities are the very thick external pyramidal layer (layer 3), the almost complete absence

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1. Bucy, P. C., and Buchanan, D. N.: Athetosis, Brain **55**:479, 1932.

2. von Economo, C., and Koskinas, G. N.: Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen, Vienna, Julius Springer, 1925.

of the internal granular layer (layer 4) and the presence of enormous pyramidal cells (Betz cells) in the internal pyramidal layer (layer 5) (fig. 1).

The premotor area (area 6 of Brodmann, the intermediate precentral region of Campbell, area FB of von Economo and Koskinas) does not differ greatly from area 4, except in the absence of the gigantic pyramidal cells of Betz. Large pyramidal cells (far smaller, however,

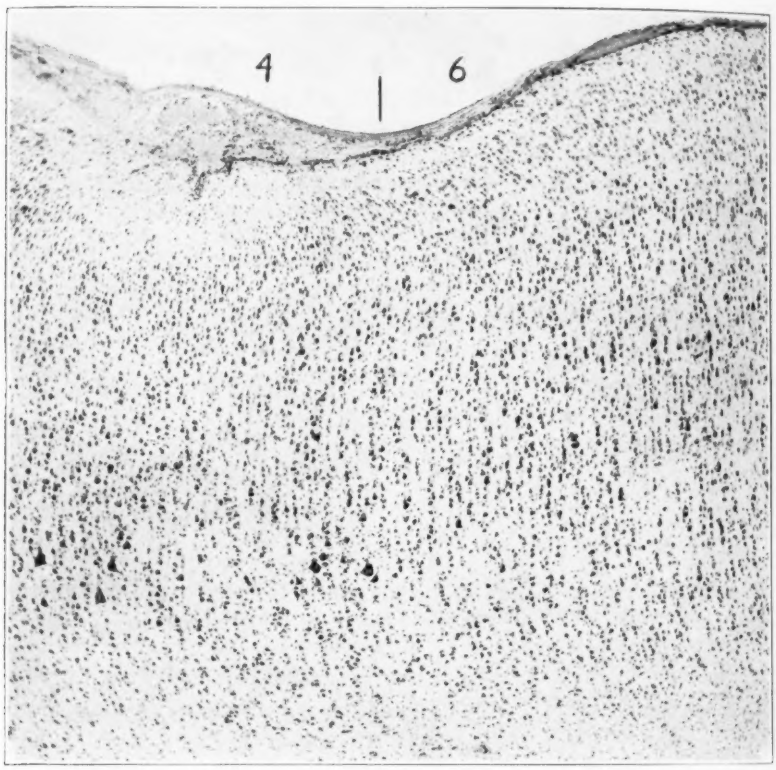

Fig. 1.—Photomicrograph of the cortex at the junction of areas 4 and 6. The striking similarity between the two except for the absence of Betz cells in area 6 is clearly shown. Toluidine blue; × 50.

than the Betz cells) are present throughout area 6. They tend to occupy a position more external in the cortex than the gigantic cells of area 4, and at times it becomes difficult to determine whether they lie in the third or the fifth layer; furthermore, the external pyramidal layer (layer 3) tends to be wider and to contain more cells than the corresponding layer in area 4.

Area 6 lies rostral to the motor area, occupying the region superior to the arcuate sulcus on the convexity of the hemisphere, and the corre-

sponding portion of the superior gyrus (gyrus marginalis) of the medial surface. (There is, in addition, a small portion of area 6 lying just oral to the face area of the motor cortex. However, as it is concerned chiefly with movements of mastication [C. and O. Vogt [3]], it will not be alluded to further in this report.) Area 6 in man occupies the greater portion of the convexity of the precentral gyrus, except in the leg area, and the posterior portions of the first and second frontal convolutions.

In view of the great microscopic similarity between areas 4 and 6, it is not surprising to learn that both are closely related and give rise together to the chief motor projection systems from the cortex, and that, within certain limits, either is capable of independent motor activity (Fulton and Kennard [4]). This was first suggested by Campbell [5] because of the microscopic similarities of the two areas and was further supported by the stimulation experiments of C. and O. Vogt,[3] who observed characteristic differences in the responses from each area. The importance of area 6, however, as an essential component of the cortical motor systems has not previously been fully appreciated, and it is to this phase of the subject that recent studies in this laboratory, of which the present report is a part, have been directed.

METHODS

In this series of experiments [6] the motor and premotor cortex of one or both hemispheres of twenty-three animals, sixteen monkeys (Pithecus [Macacus] rhesus), two baboons (Papio papio), four chimpanzees (Pan chimpanse) and one gibbon (Hylobates) were stimulated. The results in all were in essential harmony.

Anesthesia.—In previous experiments in this laboratory the majority of operations were performed under the anesthesia of one of the barbiturate derivatives (dial, sodium amytal, pentobarbital sodium and others). Fulton and Keller [7] noted that these anesthetics, though admirably suited to many experimental surgical procedures, depress in some measure the excitability of the motor cortex and almost completely suppress that of the premotor area. For that reason it was essential that some other anesthetic be used, and ether seemed most suited to our needs.

3. Vogt, C., and Vogt, O.: Allgemeinere Ergebnisse unserer Hirnforschung, J. f. Psychol. u. Neurol. **25**:273, 1919.

4. Fulton, J. F., and Kennard, Margaret A.: A Study of the Flaccid and Spastic Paralyses Produced by Lesions of the Cerebral Cortex in Primates, Tr. A. Res. Nerv. & Ment. Dis., 1932, to be published.

5. Campbell, A. W.: Histological Studies on the Localization of Cerebral Function, London, Cambridge University Press, 1905.

6. Dr. I. Bieber, Dr. Margaret A. Kennard and Dr. James W. Watts, III, assisted in the experiments; Mr. L. R. V. Kerby administered the anesthetics.

7. Fulton, J. F., and Keller, A. D.: Observations on the Response of the Same Chimpanzee to Dial, Amytal and Nembutal Used as Surgical Anaesthetics, Surg., Gynec. & Obst. **54**:764, 1932.

It is not entirely free from similar disadvantages, but by maintaining a moderately light anesthesia the excitability of these cortical areas can be maintained fairly evenly (Leyton and Sherrington[8]).

In the majority of instances an osteoplastic flap was reflected, aseptic precautions being used, exposing the greater portion of the cortex of the convexity of the hemisphere to be stimulated. Careful tracings of the cortical markings were made on cellophane (Fulton and Keller[9]). This provides an accurate map of the cerebral cortex from which detailed drawings are made and the localization of the results of stimulation carefully noted.

Stimulation.—Faradic current from a DuBois-Reymond or Harvard coil was used. The stimulation was chiefly with a monopolar electrode, the indifferent electrode being placed in the rectum. Bipolar stimulation was also used, and results identical in all respects were obtained, though localization of discrete excitable points is somewhat more difficult with the latter method.

Incision of the cortex separating areas 4 and 6 was made in the majority of instances with a sharp scalpel. Extirpations were performed by a combination of the Bovie high frequency current for thrombosing the large veins and for incision of the pia-arachnoid, a sharp scalpel for incision of the cortex and a dull spatula for completion of the extirpation. The motor and premotor areas removed, at either operation or autopsy, were fixed in alcohol and stained by the Nissl technic. These areas were then carefully studied microscopically and the cyto-architecture correlated with the results of stimulation. In suitable cases the remainder of the central nervous system was fixed in Müller's fluid,[9a] impregnated by the Marchi method, and the resultant degeneration was studied.

OBSERVATIONS

In a normal animal, under light ether anesthesia, stimulation of area 6 produces four types of movement in the extremities: (1) sustained contraction of relatively small groups of muscles in the contralateral extremities; (2) complex progressive and rhythmic movements of an entire contralateral extremity or both contralateral extremities and the tail; (3) torsion movements of the trunk and pelvis, and (4) movements of the ipsilateral extremities, principally the lower.

Motor Area.—Before discussing these various types of movement elicitable from the premotor cortex, it may be well to review the nature of the motor activity which results from the stimulation of the motor cortex as observed by numerous workers, e. g., Ferrier,[10] Beevor and

8. Leyton, A. S. F., and Sherrington, C. S.: Observations on the Excitable Cortex of the Chimpanzee, Orang-Utan and Gorilla, Quart. J. Exper. Physiol. **11**:135, 1917.

9. Fulton, J. F., and Keller, A. D.: The Sign of Babinski, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

9a. An aqueous solution of 2.5 per cent potassium dichromate and 1 per cent sodium sulphate.

10. Ferrier, D.: The Functions of the Brain, London, Smith, Elder & Co., 1876.

Horsley,[11] Sherrington and his co-workers,[12] C. and O. Vogt,[3] Foerster,[13] Fulton and Keller [9] and others, and as seen in the course of the experiments recorded here.

Stimulation of the motor area with a stimulus of slightly greater than threshold intensity gives rise to discrete sustained contractions in small groups of muscles in the contralateral extremities such as extension of the thumb or flexion of the digits. These movements are much more readily produced in the distal parts of the extremity than in the proximal. Thus, responses produced by excitation of area 4 are most commonly observed in the digits, wrist and ankle, while diffuse movements of shoulder and hip are much less commonly observed. The movement seldom involves more than one joint and is usually maintained throughout the duration of the stimulus, seldom persisting afterward with threshold stimuli. With strong stimulation of long duration, rhythmic movements, which persist after the termination of stimulation in an epileptiform after-discharge, may readily be observed in the normal brain (Sherrington and his co-workers). In the presence of scarring of the neighboring cortex, less intense stimulation may produce similar clonic after-discharge.

Maintaining the stimulus near threshold intensity, one finds by carrying it forward on the surface of the precentral area that responses will be obtained up to a line from 5 to 7 mm. anterior and parallel to the central sulcus. Beyond this line the cortex is unresponsive. This line marking the anterior limits of motor excitability to threshold stimuli corresponds accurately with the anterior limits of area 4 as shown by

11. Beevor, A., and Horsley, V.: A Minute Analysis (Experimental) of the Various Movements Produced by Stimulating in the Monkey Different Regions of the Cortical Centre for the Upper Limit, as Defined by Professor Ferrier, Phil. Tr. Roy. Soc., s.B **178**:153, 1887; A Further Analysis by Electric Stimulation of the So-Called Motor Region of the Cortex Cerebri in the Monkey (Macacus Sinicus), ibid. **179**:205, 1888; A Record of the Results Obtained by Electrical Excitation of the So-Called Motor Cortex and Internal Capsule in an Orang-Outang (Simia Satyrus), ibid. **181**:129, 1890.

12. Brown, T. G., and Sherrington, C. S.: (*a*) On the Instability of a Cortical Point, Proc. Roy. Soc., s.B **85**:250, 1912. (*b*) Observations on the Localization in the Motor Cortex of the Baboon (Papio Anubis), J. Physiol. **43**:209, 1911; (*c*) Note on the Functions of the Cortex Cerebri, ibid. **46**:xxii, 1913. (*d*) Grünbaum, A. S. F., and Sherrington, C. S.: Observations on the Physiology of the Cerebral Cortex of Some of the Higher Apes, Proc. Roy. Soc., s.B **69**:206, 1901; (*e*) Observations on the Physiology of the Cerebral Cortex of the Anthropoid Apes, ibid. **71**:152, 1903. (*f*) Roaf, H. E., and Sherrington, C. S.: Experiments in Examination of the "Locked-Jaw" Induced by Tetanus Toxin, J. Physiol. **34**:315, 1906. (*g*) Mott, F. W.; Schuster, E., and Sherrington, C. S.: Motor Localization in the Brain of the Gibbon Correlated with a Histological Examination, Proc. Roy. Soc., s.B **84**:67, 1911. (*h*) Leyton and Sherrington.[8]

13. Foerster, O.: The Cerebral Cortex in Man, Lancet **2**:309, 1931.

C. and O. Vogt and as determined in these experiments. As has been previously stated, a similarly limited area is excitable under the barbiturate anesthetics. This is extremely well shown by comparing the results of stimulation of the brain of the gibbon under ether anesthesia recorded by Mott, Schuster and Sherrington [12g] with those obtained by Fulton and Keller [9] on the brain of an animal of the same genus but under dial anesthesia. In the former instance, numerous responses of the type soon to be described were obtained from the premotor area, while in the latter case the cortex lying anterior to the motor area was almost inexcitable.

Premotor Area.—1. Sustained Movements: If the intensity of the stimulus is now increased over that required to delimit the motor area, usually by bringing the coils of the inductorium about 0.5 to 1 cm. closer together, motor response will be obtained from that portion of the cortex lying just anterior to the motor area, i. e., the posterior part of area 6. These responses are similar in many respects to those obtained from area 4. They are sustained and tend to involve relatively small groups of muscles, though they are more extensive than the movements from the motor area and have little tendency to after-discharge. The localization of movement is comparable to that of the motor area, although less discrete. Thus, the area which gives rise to movements of the hip and knee lies directly anterior to the representation of the lower extremity in the motor cortex, and the same is true for the contralateral upper extremity. (Movements of the face and of mastication were not closely examined in the present experiments.)

If a very superficial incision from 1 to 2 mm. deep (fig. 2) is made separating areas 4 and 6 along the boundary previously determined, the excitability of the premotor area for these sustained movements is lost, while the motor area remains excitable, even up to the posterior limits of the incision. The excitability of the latter may even be enhanced, since responses are often more easily elicited and are more extensive, but the actual threshold is rarely affected. Moreover, undercutting of the premotor area in order to destroy any downward projection fibers while leaving intracortical fibers intact does not abolish these responses from area 6. Thus it would seem safe to conclude that these movements elicited from the premotor area are due to excitation of nervous elements present there and not to "spread" of the electrical stimulus to the motor cortex, which should occur quite as readily in the presence of this superficial incision as in the normal brain. In addition, it would seem that the axons of the responsible neurons in the premotor cortex pass to the motor area through the superficial layers of the cortex. Whether these fibers terminate about the cells of area 4 and transfer their impulses to second neurons, possibly the pyramidal tract, for further

transmission or merely pass through area 4 to lower centers has not yet been determined.

2. Complex Progressive and Rhythmic Movements: If the intensity of the stimulus is again increased slightly, the premotor cortex, for a distance of about 1 cm. anterior to the boundary between areas 4 and 6, is excitable and gives rise to an entirely different type of movement. This anterior limit of the portion of the premotor area responsible for movement in contralateral extremities corresponds quite accurately with the boundary between areas 6a α and 6a β as described by C. and O. Vogt,[3] but we have been unable to convince ourselves that it can be identified by any definite histologic difference in area 6.

These movements are really of two types, the progressive and the rhythmic, although the former may pass into the latter with prolonged stimulation. They usually involve all joints of one contralateral extremity or both contralateral extremities and even the tail. The

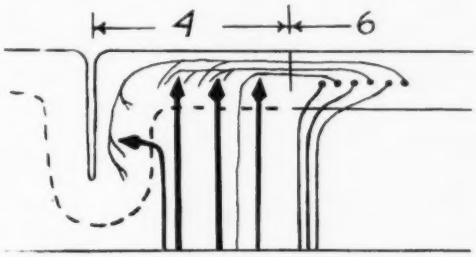

Fig. 2.—A diagrammatic section of the cortex of areas 4 and 6 illustrating the probable course of fibers from area 6. The Betz cells and the pyramidal fibers are indicated by coarse black figures. Three courses of fibers from area 6 are shown, one which passes to area 4 but descends to lower levels, one which terminates about the cells of area 4, and one which descends directly from area 6.

movements are almost invariably complex, since they involve various types of movements—extension, flexion, adduction, abduction, internal and external rotation and inversion and eversion. In the progressive type, the extremity passes successively through the various phases of movement. At times these movements seem to exhibit a grotesque form of purposeful activity. At other times this apparent purposeful character is absent, and the movements partake of the nature of the involuntary movements which result from a diseased nervous system. Because of the complex nature of the movements, accurate and complete descriptions are difficult. These movements do not give rise to after-discharge but stop with the cessation of stimulation.

The rhythmic type of movement may follow the progressive just described or may be instituted initially. Although they may involve several joints, these movements are less complex. They consist of alter-

nating extension and flexion or, less commonly, abduction and adduction, and are not progressive through various phases of movement, but are only a constant clonic repetition. Even with stimulation of short duration they tend to outlast the stimulus for several seconds. Clonic epileptiform after-discharge of this character is elicited with far greater ease from the premotor area than from area 4. The similarity of this form of response to certain cases of spontaneous jacksonian epilepsy of man and monkey is striking. Both types of complex response have a distinct period of latency as compared with movement elicited from the motor area.

Movement of the tail may be associated with either of these types of complex movement and is commonly quite stereotyped. It most often consists of flexion of the tail to the contralateral side, and may at times be rhythmic.

A superficial incision between areas 4 and 6, as previously described, greatly reduces the ease with which these responses are elicited, but does not abolish them as in the first type of response described. The same is true of extirpations of the motor area (the completeness of which has been determined by microscopic study). In a number of cases the brain was reexposed two or more weeks after the extirpation of the motor area and the persistent excitability of the premotor cortex demonstrated.

The counterpart of this experiment, i. e., undercutting area 6 to destroy any downward projection fibers while leaving its transcortical connections with area 4 and the projection system of the latter uninjured, largely abolishes these complex movements, while the sustained movements previously described are left intact.

The fact that movements can be elicited from area 6 in the absence of the motor cortex would seem conclusive evidence that the premotor cortex is provided with its own projection system independent of the axons of the Betz cells. Whether these fibers terminate on secondary neurons in subcortical centers, which, in turn, conduct the impulses down the spinal cord, or are a long fiber system comparable to that of the Betz cells is at present being investigated.

That an incision of the cortex separating areas 4 and 6 or extirpation of area 4 depresses the activity of the premotor cortex in the production of complex contralateral movements is not so easily interpreted. It is possible that the incision or extirpation damages long projection fibers from this area but, in view of the fact that a superficial incision, 2 or 3 mm. deep, is effective this would seem unlikely. We are inclined to believe that this is evidence that the complex movements in part, like the first type of movement described, are mediated by short fibers which pass to the motor cortex and there exert their influence via the pyramidal system.

Little localization of this type of response is detectable in the premotor cortex, as stimulation of one point gives rise to movement at all joints in one extremity and even of both extremities and the tail. However, the repeated stimulation of one point usually gives rise to the same response. In addition, the portion of the premotor area anterior to the leg area of the motor cortex always gives rise to movement of the contralateral leg whether it evokes movement of the arm or not. On the other hand, stimulation of the portion anterior to the arm area of the motor cortex always gives rise to movement of the contralateral upper extremity, frequently without involvement of the leg. (Stimulation of the cortical area immediately anterior to that giving rise to complex contralateral movements in the extremities evokes rotation of the head, deviation of the eyes to the opposite side and dilatation of the pupils. These responses have not been carefully studied in these experiments although they have been observed.)

3. Torsion of the Trunk and Pelvis: Stimulation of the premotor area in the neighborhood of the precentral sulcus, with stimuli of the same or greater intensity than that necessary to elicit the complex contralateral movements, frequently elicits torsion movements of the trunk and pelvis. The movements of the trunk are most readily elicited from just below the precentral sulcus and most commonly consist of a bending of the trunk along its long axis with the concavity toward the side opposite the area stimulated. These movements have a rather long latency, and are slow in development. They are usually sustained, although rhythmic movements have been observed.

Torsion of the pelvis is most readily elicited from the superior lip of the precentral sulcus and consists of rotation of the pelvis about the long axis of the body, with dorsal elevation of the contralateral hip and ventral depression of the ipsilateral. These movements may be sustained or rhythmic and, when seen in association with movements of the trunk, as not infrequently occurs, present a peculiar writhing of the lower half of the body. Such movements are also commonly associated with complex movements of the contralateral extremities which partake particularly of flexion, and at times with movements of the ipsilateral lower extremity, which are largely extensor.

Incision of the cortex separating areas 4 and 6 and extirpation of area 4, while they may lessen the ease with which these movements are elicited, do not abolish them. Thus one must conclude that these movements, too, are mediated over a projection system from area 6 independent of the pyramidal system of area 4.

4. Ipsilateral Movements: As these responses are to be reported in much greater detail in a later paper, they will be mentioned only briefly here.

That ipsilateral movements could be elicited from the premotor area does not come as a complete surprise. C. and O. Vogt [3] mentioned similar results in the briefest fashion; Foerster [13] suggested that the caudal segments of the body are represented bilaterally in the cortex, and Fulton and Keller [9] showed that removal of both "leg areas" of the motor cortex, which extirpations usually included the posterior part of area 6, produces a much greater deficit in a given extremity than removal of only the contralateral cortical area.

Movements of the ipsilateral extremities are most readily elicited from a small area, from 2 to 3 mm. in diameter, in about the middle of the superior lip of the precentral sulcus, i. e., in the posterior half of area 6. At times a larger area, from 5 to 6 mm. in diameter, surrounding this most excitable point may also give rise to ipsilateral movement, but never as extensively or as readily as the smaller area. The movements elicited generally involve the lower extremity only and are almost always extensor, although flexor responses and movement of the ipsilateral upper extremity alone or in conjunction with the lower have been occasionally observed.

Separation of area 6 from area 4 or destruction of the latter not only does not abolish the ipsilateral response but commonly enhances it. That the movement is not due to spread of the stimulus to the opposite hemisphere is attested by several facts: (1) It is not elicitable from that portion of the cortex nearest the opposite hemisphere or by stimulation of the falx cerebri; (2) undercutting of the premotor area in order to destroy the downward projection fibers from this area completely abolishes it; (3) it can be obtained after removal of the opposite motor and premotor areas.

The threshold of the ipsilateral response is commonly slightly higher than that for the contralateral complex movements. The pathway of conduction must be independent of the motor area, but its exact course is unknown and is being investigated.

The ipsilateral responses seem the most susceptible to the barbiturate anesthetics of all manifestations evoked from area 6. A small dose of dial (0.4 cc. per kilogram in a small monkey), insufficient to suppress completely all spontaneous movement, will abolish all trace of the ipsilateral response.

ILLUSTRATIVE EXPERIMENTS

The following six experiments were selected as illustrative of the points previously discussed. The experimental animals include two monkeys (Pithecus [Macacus] rhesus), one baboon (Papio papio), two chimpanzees (Pan chimpanse) and one gibbon (Hylobates lar). These experiments demonstrate all of the points except torsion of the trunk and pelvis, which has been observed only in the monkey and was not

specifically noted in these two cases. In the first operation of experiment 4, in experiment 5 (both chimpanzees) and in experiment 6 (gibbon), sodium amytal was used as the anesthetic. The first operation in experiment 4 was performed before it was realized that anesthetics exerted a differential influence on the cortex of area 6. In the other two instances the size or value of the animals, or both, made sodium amytal (a safer anesthetic in animals) the drug of choice. Fortunately, in all of these instances the anesthesia was not sufficiently deep to depress completely the excitability of the premotor cortex.

EXPERIMENT 1.—*Immature monkey (Pithecus [Macacus] rhesus); weight, 1,450 Gm.; ether anesthesia; faradic stimulation of motor area with typical discrete sustained responses; determination of anterior limit of area 4; stimulation of area 6; higher threshold; production of sustained contractions, complex movement and ipsilateral responses; incision of cortex between areas 4 and 6; abolition of sustained and ipsilateral responses; complex movements still present.*

The subject of this experiment was a small immature animal, somewhat emaciated, but exhibiting no evidence of neurologic abnormality.

Anesthesia.—Ether was administered by the drop method throughout the operation. The anesthesia was quite light and kept at a nearly constant level. The corneal reflexes were present at all times, and the state of narcosis was just sufficient to abolish all spontaneous movements.

Operation (Feb. 13, 1933).—An osteoplastic flap was reflected, exposing the greater portion of the left cerebral hemisphere. The cortical markings were traced on cellophane and copies of this tracing made (fig. 3). Accurate records were kept of the points stimulated, of the intensity of stimulus (recorded in the number of centimeters by which the coils of the inductorium were separated) and of the results obtained. Monopolar faradic stimulation was used. With a stimulus of 13 cm., just about threshold strength, we were able to delimit the motor area. The motor responses were discretely localized in the cortex and were of the usual type of sustained contractions in small muscle groups, with little latency and no after-discharge, and were most easily elicited for distal parts of the extremity.

The threshold of the premotor area was 11.5 cm., distinctly higher than that of area 4. With stimuli of this intensity, responses not unlike those obtained from the motor cortex could be elicited from the posterior part of area 6. They were sustained contractions with no tendency toward after-discharge but had a rather longer period of latency, were more extensive and tended to involve the proximal joints of the extremity. Like responses obtained from area 4, all movement was in the contralateral extremities. The intensity of stimulus was then raised, and with the secondary coil at 10 and 10.5 cm. complex synergic movements were produced in the contralateral extremities. The complexity of movement was so great —the several joints of one extremity, or at times of both, being simultaneously involved—that accurate and complete description became almost impossible. These complex movements might proceed from one phase of activity to another and be thus termed progressive, or rhythmic clonic movements might occur. In the progressive type one might observe extension of the digits, then flexion of the ankle and digits, followed by internal or external rotation of the entire extremity associated with movement at hip and knee. In the rhythmic type, alternation of flexion and extension of one or more joints was most common.

From a point just above the precentral sulcus, deviation of the tail to the right and movement of the ipsilateral (left) lower extremity could be obtained. The threshold for these movements was even higher, requiring a stimulus of 9.5 cm. However, the response was from a sharply localized area in the cortex, and even with stronger stimulation could not be elicited from other areas.

A superficial incision, about 2 mm. deep, was then made with a sharp scalpel along the previously determined boundary between areas 4 and 6. Following this, the sustained responses could no longer be obtained from the premotor cortex, and while the complex movements were still elicitable the threshold had been raised to 9.5 cm. The animal was subsequently killed, and microscopic study of the cortex showed that the line of incision corresponded accurately with the boundary between areas 4 and 6, except in the uppermost part of the leg area where a few Betz cells could be found anterior to the incision. The accompanying copy of the tracing (fig. 3) shows in more detail the points stimulated and typical examples of the responses obtained.

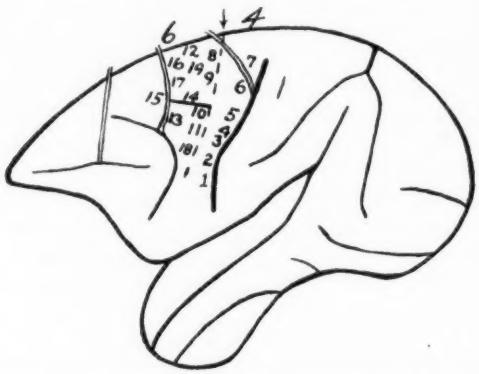

Fig. 3 (experiment 1).—A tracing of the cortical markings of the left hemisphere. A broken line indicates the boundary between areas 4 and 6 along which a superficial incision was made. Representative results of stimulation are indicated by the figures. With a stimulus of from 12.75 to 13 cm.: *1,* movement of the lips on the right side; *2,* flexion of the right thumb; *3,* pronation of the right hand; *4,* extension of the right fingers; *5,* flexion of the right fingers; *6,* flexion of the right hip; *7,* flexion of the right toes. With a stimulus of 11.5 cm.: *8,* extension of the toes of the right foot; *9,* sustained flexion of the right knee and hip; *10,* pronation of the forearm and flexion of the digits; *11,* flexion of the elbow. With a stimulus of 10.5 cm.; *12,* complex movements including inversion of the right foot with flexion of the ankle and digits; *13,* complex movement with flexion of the right elbow and digits. With a stimulus of 9.5 cm.: *14,* eversion of the ipsilateral foot and movement of the digits and flexion of the tail to the right; *15,* rhythmic movements of the right ankle; *16,* rhythmic movements of the right ankle and the right wrist and fingers; *17,* complex movement including internal rotation of the right arm at the shoulder, flexion of the knee and plantar extension of the foot. An incision was made between areas 4 and 6. With a stimulus 9.5 cm.: *18,* clenching of the right fist, internal rotation of the arm and flexion of the elbow; *19,* external rotation of the right arm, clenching of the fist, flexion of the hip, knee and ankle and external rotation of the hip.

EXPERIMENT 2.—*Immature monkey; weight, 1,450 Gm.; ether anesthesia; left motor area previously removed; right hemisphere exposed; faradic stimulation of motor area produced discrete sustained contralateral responses; stimulation of area 6; higher threshold; evoked similar sustained responses, less isolated and with greater latency; more intense stimuli produced complex progressive and rhythmic movements; superficial incision between areas 4 and 6 abolished sustained responses and depressed complex ones.*

On Jan. 12, 1933, the left motor area of this animal had been extirpated. Following this procedure the animal suffered from the usual flaccid hemiplegia, from which it had partially recovered at the time of the present experiment.

Anesthesia.—As usual, ether was used and the anesthesia maintained fairly light throughout the experiment.

Stimulus.—The stimulus was the usual faradic current supplied by a DuBois-Reymond inductorium. A monopolar electrode was used on the cortex, and the indifferent electrode was placed in the rectum. The intensity of the stimulus is indicated as the distance in centimeters to which the secondary coil was withdrawn.

Operation (February 23).—The motor and premotor areas of the right hemisphere were exposed by reflecting the scalp and removing the overlying bone with a rongeur. The cortical markings were traced on cellophane (fig. 4).

Motor Area.—The threshold was 13 cm. and the responses were of the usual well localized, discrete, sustained type. The anterior limit of the motor area was found to lie from 5 to 7 mm. anterior to the central sulcus, being farthest anterior in the leg area. Even with intense prolonged stimulation, it was impossible to produce rhythmic responses or after-discharge from the motor cortex.

Premotor Area.—The threshold of this area for sustained responses comparable to those from area 4 was 12 cm. They were elicitable from the posterior 5 mm. of area 6 and were similar to those from the motor area, except for a longer latency and a tendency to involve more muscle groups. With stimuli of 11.5 cm. complex synergic rhythmic and progressive movements were evoked in the left (contralateral) upper and lower extremities and in the tail. That portion of area 6 below the precentral sulcus always gave rise to movement in the upper extremity and frequently in the lower as well, while the area above the sulcus always gave rise to movement in the lower extremity and commonly in the upper extremity and tail at the same time. This was the only evidence of localization obtainable for the complex movements. The rhythmic movements were readily elicited and frequently after a weak (11.5 cm.) stimulus of brief duration would continue in typical epileptiform after-discharge for several seconds.

Incision.—After these observations were made, a superficial incision, from 1 to 2 mm. deep, was made along the previously determined boundary between areas 4 and 6 (fig. 4). Immediately after the incision was made, the excitability of area 6 was greatly depressed, although the excitability of area 4 was unaffected. It became impossible to elicit the sustained responses from area 6, but the complex ones were still present and unaltered in type, although a stronger stimulus was required for their production.

Comment.—These two examples of the results of stimulation of the motor and premotor areas in the monkey are fairly typical for the sixteen animals of this type examined. The disappearance of the sustained responses from the posterior part of area 6 after a superficial

incision separating area 6 from 4 is in entire agreement with all other experiments and would seem quite adequate proof that this response is mediated by way of fibers which pass from the premotor to the motor area in the superficial cortical layers. Whether these fibers terminate about the cells of area 4, as we are inclined to believe, or only pass through that area to lower centers, as yet awaits proof.

This same incision produces depression but not abolition of the complex contralateral movements, and this would seem to be evidence that these movements are produced by impulses traveling both over fibers direct from area 6 to lower centers and over fibers which pass to or by way of area 4. It is not impossible that in the motor cortex the impulses are transferred to other neurons and are eventually

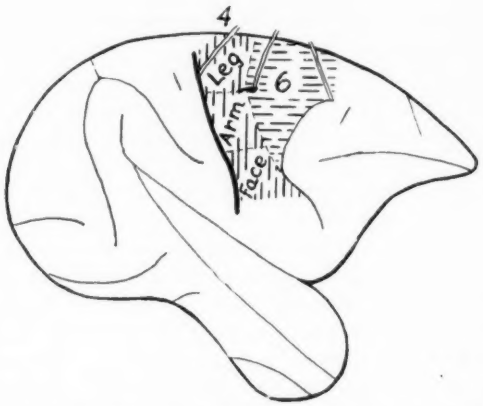

Fig. 4 (experiment 2).—Tracing of the right hemisphere. Area 6 is marked by horizontal lines; area 4, by vertical broken lines.

delivered at the final common path by the axons of the Betz cells themselves (pyramidal tract).

The abolition of the ipsilateral response observed in experiment 1 is, on the other hand, not a common result of such an incision, the response usually being augmented by isolation of area 6 from 4. In this connection it must be borne in mind that this response has the highest threshold of all those elicitable from the premotor cortex and is the most susceptible to anesthetics, ether as well as the barbiturates. With ether anesthesia slight increases have frequently been observed to suppress the response completely for several minutes.

All of these observations agree with those found in the monkey (Cercopithecus) by C. and O. Vogt,[3] although in many respects one might wish for somewhat more detail in their report of the results of stimulation.

EXPERIMENT 3.—*Immature male baboon (Papio papio); weight, 4,300 Gm.; ether anesthesia; monopolar faradic stimulation, with typical responses from motor and premotor areas, including movement in the ipsilateral lower extremity; incision of cortex between areas 4 and 6 with depression of contralateral and augmentation of ipsilateral responses from area 6; extirpation of area 4 with preservation of ipsilateral response. (Premotor series, no. 13.)*

This animal was a small, very active, healthy male baboon (Papio papio).

Anesthesia.—Ether was administered by the open drop method and anesthesia was quite light throughout the operation.

Operation (Feb. 24, 1933, with the assistance of Dr. Margaret A. Kennard).—An osteoplastic flap was reflected, exposing the left cerebral hemisphere, and the cortical markings were traced on cellophane (fig. 5).

Stimulus.—After an initial period, during which the motor area was relatively inexcitable, a threshold of 12 cm. was obtained. The responses from the motor

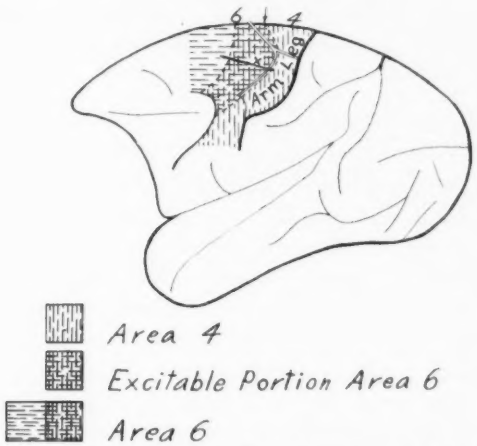

Fig. 5 (experiment 3, baboon).—Tracing of the cortex showing areas 4 and 6 as determined by stimulation and confirmed by microscopic study. The anterior limit of the excitability of area 6 for movement of the extremities is shown. X indicates the point from which ipsilateral responses were most readily elicited.

area were the usual sustained contractions in small groups of muscles, principally in the hand, foot, ankle and wrist. They were, of course, limited to the contralateral extremities. The anterior margin of the motor area was readily determined. With stimuli of 10.5 and 11 cm., similar sustained responses were obtainable from the posterior part of area 6. They were less discrete and tended to involve the proximal parts of the extremity much more than those elicited from area 4.

Stimuli of greater intensity, 9 and 10 cm., gave rise to slow complex synergic movements in the contralateral upper and lower extremities and movement of the tail. From the upper half of the premotor area responses in the contralateral arm and leg and in the tail were obtained simultaneously. The same was true in that portion of the premotor area anterior to the arm area, but to a less marked degree. These movements had a definite latency and were slow and progressive. With still more intense stimulation, from 9 to 9.5 cm., from a small area about

1 mm. in diameter on the superior lip of the precentral sulcus responses of the tail and ipsilateral lower extremity were obtained. These were associated with movement in the contralateral lower extremity. Movements of the tail, which usually were the first to appear, were rhythmic movements from side to side. The responses evoked in the ipsilateral lower extremity were slow extension of the hip and knee and plantar flexion of the foot. Movements of the contralateral extremity were usually extensor but at times were quite complex.

Incision.—A superficial incision, about 2 mm. deep, was made with a sharp scalpel separating areas 4 and 6. Following the incision, the excitability of area 6 for contralateral movements was greatly depressed. The sustained movements were abolished, while the complex contralateral movements, though still obtainable, were much less easily elicited. However, the movement of the tail and ipsilateral lower extremity were present with much increased vigor.

Extirpation.—The entire leg and arm areas of the motor cortex were then removed with a sharp scalpel. For a short time the excitability of area 6 was completely suppressed, but it soon returned to the condition present following the incision, except that the contralateral responses were still less active. The ipsilateral responses remained and were very vigorous.

Comment.—These observations on the excitability of the premotor area are of particular interest because the cortex of the baboon has not often been subjected to electrical stimulation. Graham-Brown and Sherrington,[12b] operating on a baboon (Papio "anubis") under deep chloroform and ether anesthesia, found only the motor area excitable, although Sherrington and his co-workers [12g] elicited responses from the premotor area of the gibbon and mentioned the variability of the anterior margin of the excitability in the chimpanzee under chloroform and ether anesthesia and commented on the fact that stimulation of the cortex anterior to the region of the Betz cells gave rise to motor responses. Fulton and Keller,[9] in operating on many baboons (Papio papio, Papio hamadryas and Papio cynocephalus) under various barbiturate anesthetics, obtained no responses from the premotor cortex.

EXPERIMENT 4.—*Immature chimpanzee (Pan chimpanse); weight, 21 Kg. First operation: sodium amytal and ether anesthesia; monopolar faradic stimulation with responses from area 6; extirpation of arm area and part of area 6. Second operation: ether anesthesia; usual response from intact motor area; complex synergic movements in contralateral leg, nothing in arm from area 6; epileptiform after-discharge in leg; incision between areas 4 and 6; area 6 inexcitable. ("Mussai.")*

First Operation (May 13, 1932, by Dr. J. F. Fulton).—A total of 17.5 cc. of a 10 per cent solution of sodium amytal (1.75 Gm.) was administered intraperitoneally but even so the anesthesia was light, and at times a small quantity of ether had to be given. An osteoplastic flap was reflected, exposing the lateral surface of the right cerebral hemisphere.

The cortex (fig. 6) was then stimulated with the monopolar electrode. With stimuli of 10.5 cm., the motor area was excitable, and its margins were readily outlined. When the intensity of the stimulus was elevated to 9.5 cm., it was possible to produce fairly marked responses of both the upper and the lower extremi-

ties at points well anterior to the frontal boundary of the arm and leg areas. Unfortunately, no description of the movements elicited from the premotor area is available. Following these observations the arm area and a large portion of area 6 lying anterior to it were extirpated. That the extirpation extended well beyond area 4 is confirmed by microscopic study.

Second Operation (Jan. 16, 1933, by Dr. J. F. Fulton).—Anesthesia: Ether was administered by the open, drop method throughout.

The old osteoplastic flap was reelevated. The site of the previous extirpation was occupied by a shallow, yellowish-white, scarred depression. With the monopolar electrode, the threshold for the leg area of the motor cortex proved to be 12 cm. The crater of the old lesion was inexcitable. Stimulation of the leg area gave exquisitely localized responses, principally in the distal part of the extremity, and with this intensity of stimulus the anterior limit of this area was readily determined. Stimulation of the premotor area with somewhat more intense stimuli (10 cm.) gave rise to diffuse responses of the contralateral (left) lower

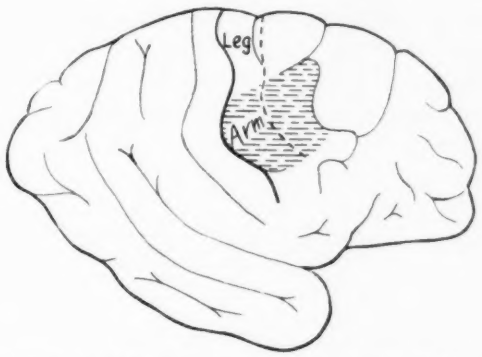

Fig. 6 (experiment 4, chimpanzee).—Tracing of the right hemisphere. The boundary between areas 4 and 6 is indicated by a vertical broken line. The region extirpated at the first operation is shaded by broken horizontal lines.

extremity, generally involving the musculature of the whole extremity. These responses were obtained over a large area extending from 20 to 25 mm. anterior to the motor cortex. No movements in the left upper extremity were observed. However, stimulation of the cortex just anterior to the crater of the old lesion in the arm area gave rise to rhythmic movements in the left lower extremity, which persisted long after the termination of the stimulus in an epileptiform afterdischarge. An incision about 2 mm. deep was then made with the Bovie cutting current between areas 4 and 6, and following this area 6 was inexcitable even with stimuli of great intensity.

EXPERIMENT 5.—*Mature chimpanzee; weight, 27.7 Kg.; sodium amytal anesthesia; monopolar faradic stimulation with typical sustained discrete movements from the motor cortex and slow complex movements from area 6—additional sodium amytal abolished the excitability of premotor area. ("Sambo.")*

This was a large, healthy, male chimpanzee which had only recently matured.

Anesthesia.—Following an ether and chloroform induction, 20 cc. of a 10 per cent solution of sodium amytal was administered intraperitoneally (2 Gm. or 72 mg. per kilogram). This was quite a light anesthesia.

Operation (Jan. 30, 1933, by Dr. J. F. Fulton).—A left-sided osteoplastic flap was reflected. After the cortical markings were traced on cellophane in the usual manner, the cortex was stimulated with a monopolar electrode. The threshold of the motor area was 11.5 cm., and with this strength of stimulus the anterior limits were precise. From the leg area discrete movements could be elicited at all joints—digits, ankle, knee and hip—but were most readily obtained in the ankle and the foot. Comparable results were obtained from the arm area in the upper extremity.

Anterior to the motor cortex somewhat more intense stimuli elicited diffuse slow movements involving the musculature of an entire extremity. Movements of the lower extremity were obtained from the superior part of the premotor cortex, and movements of the upper extremity from the inferior. On occasion, movements occurred in both extremities simultaneously from the same point. At this stage of the operation the animal's condition made administration of additional amytal essential. This suppressed the excitability of area 6 and made further observation impossible.

Comment.—Leyton and Sherrington [8] elicited motor responses from the premotor cortex of the chimpanzee, but no detailed study of the response was made. Fulton and Keller [9] elicited responses from the motor area only. They were, however, using barbiturates for anesthesia. Fortunately, in the operations in experiments 4 and 5, in which amytal was used as the anesthetic agent, the animals were so lightly anesthetized that the premotor area remained excitable. The depressing effects of these anesthetics on premotor excitability was well demonstrated after the additional dose required in the second animal during the course of the experiment.

In the one experiment in which ether was used, the inferior part of the premotor area had been severely traumatized by the original operation, thus interfering with its responses. The abolition of all responses from area 6 after the incision of the cortex separating areas 4 and 6 need not necessarily be of significance in this animal as it was performed with the Bovie cutting current (a much safer and more nearly bloodless procedure than the use of a scalpel). In other instances great depression of the cortex, both motor and premotor, but particularly the latter, has been observed to follow the extensive use of the cutting current even at some distance from the area.

In spite of all these difficulties, these experiments conclusively demonstrate the excitability of area 6 in these higher primates and also that, in general, this follows closely the results obtained in the monkey and baboon. The other two chimpanzees examined presented essentially the same picture.

EXPERIMENT 6.—*Immature male gibbon (Hylobates lar); weight, 1.9 Kg.; sodium amytal and ether anesthesia; monopolar faradic stimulation with elicitation of movement from areas 4 and 6; incision of cortex between with rise in threshold of area 6; undercutting of area 6 with abolition of excitability.*

This animal was small, with a gray coat and black feet and face. It was extremely affectionate and apparently in excellent physical condition, except for a certain awkwardness that was interpreted as the result of previous rickets.

Anesthesia.—One and five-tenths cubic centimeters of a 10 per cent solution of sodium amytal was injected intraperitoneally. However, as this provided an anesthesia of insufficient depth ether had to be given.

Operation (Feb. 27, 1933, by Dr. J. F. Fulton).—A left-sided osteoplastic flap was reflected, and the cortical markings were traced on cellophane.

Stimulation.—With the indifferent electrode in the rectum, monopolar stimulation of area 4 revealed a threshold of 12 cm. The movements were identical with those elicited in the other experiments. The anterior margin was readily determined. With stimuli of slightly greater intensity, complex contralateral responses were regularly elicited from a large premotor area. On a few occasions movements were observed in the ipsilateral lower extremity; however, because of the lightness of the anesthesia it could not be positively determined whether or not these were spontaneous. An incision about 3 mm. deep was then made separating areas 4 and 6. Subsequently area 4 seemed much more excitable and presented a tendency toward epileptiform after-discharge. The premotor area was less excitable than prior to the incision but, with stimuli of 10 cm., slow complex contralateral movements were readily obtained. The premotor cortex was then undercut from its anterior margin backward and this completely abolished all excitability in this area.

Comment.—Gibbons are rare occupants of physiologic laboratories, and relatively few have been the subjects of cortical stimulation. The two carefully reported studies demonstrate several of the points brought out in the other species of primates already discussed.

Mott, Schuster and Sherrington,[12g] experimenting on a black male gibbon under chloroform anesthesia, elicited the usual discrete sustained responses from the motor area. Stimulation of the premotor area evoked diffuse complex responses in the contralateral extremities. The identity of these areas was confirmed by careful microscopic study. Fulton and Keller,[9] on the other hand, operated on two gibbons under dial anesthesia, and found only the motor area excitable.

In the present experiment the only point other than those demonstrated in the preceding observations is that undercutting area 6 abolished all responses which remain after the cortex between areas 4 and 6 has been superficially incised (fig. 2). This is entirely in accord with numerous experiments on monkeys (Pithecus rhesus) in which we have had occasion to demonstrate that undercutting alone abolishes the complex contralateral movements and the ipsilateral responses while leaving the sustained contralateral responses intact. Thus, further evidence is afforded that the complex contralateral movements, at least in part, and the ipsilateral manifestations in their entirety are mediated by way of direct projection fibers which are independent of area 4, while the reverse is true of the sustained responses.

Throughout this report I have repeatedly emphasized the effect of various anesthetic drugs on the elicitation of responses from area 6, and not without purpose. There is a body of evidence[14] that the barbiturate anesthetics (dial, sodium amytal, pentobarbital sodium and others) are chiefly effective in the subcortical cerebral centers. If this is true, it may be considered as partial evidence that the downward projection system of the premotor area, unlike that of the motor, terminates in the subcortical nuclei, whose neurons continue the transmission of its impulses. Anatomic studies of this point are progressing in cooperation with Dr. Stephen Poljak of the University of Chicago.

CONCLUSIONS

1. Stimulation of area 6 of the primate brain gives rise to: (*a*) Sustained contractions of moderately small groups of muscles in the contralateral extremities. These responses are mediated by fibers which pass to the motor cortex.

(*b*) Complex progressive and rhythmic movements in the contralateral extremities, which are effected at least in part by fibers which are direct projections of area 6, independent of the motor cortex.

(*c*) Responses in the ipsilateral extremities, principally the lower ones, and the tail.

(*d*) Torsion movements of the trunk and pelvis.

2. The threshold of area 6 is higher than that of area 4, becoming increasingly greater for each of the four types of response in the order listed, except for *c* and *d* which are essentially the same.

3. The responses of area 6 are much more susceptible to anesthetic drugs, especially the barbiturates, than the responses of area 4.

4. The movements elicited from the premotor area are much more prone to pass into epileptiform after-discharge than those evoked from the motor cortex.

DISCUSSION

Dr. John F. Fulton, New Haven, Conn.: I believe that Dr. Bucy intended to mention that these observations on the premotor cortex were carried out under light ether anesthesia. It is rather significant that the barbiturates, which leave the excitability of area 4 unimpaired, completely destroy the excitability of area 6. This indicates that the projection systems from area 6 have synapses in the basal regions, red nucleus, hypothalamus, etc., on which the barbiturates are known to act.

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14. Fulton, J. F.; Liddell, E. G. T., and Rioch, D. McK.: "Dial" as a Surgical Anaesthetic for Neurological Operations; with Observations on the Nature of Its Action, J. Pharmacol. & Exper. Therap. **40**:423, 1930. Keller, A. D., and Fulton, J. F.: The Action of Anaesthetic Drugs on the Motor Cortex of Monkeys, Am. J. Physiol. **97**:537, 1931.

There is one further point of interest. The work of extirpation that Dr. Bucy referred to has allowed us to distinguish the pure pyramidal tract signs from the signs that result from lesions in area 6, and I should like to summarize those briefly.

In the chimpanzee Dr. Kennard and I have observed that lesions sharply restricted to area 4 give rise to a flaccid paralysis, depression of tendon reflexes and a simple extensor Babinski reaction.

Lesions restricted to area 6, on the other hand, give rise to a grave motor deficit with strong spasticity, an increase in tendon reflexes, the positive Rossolimo response (which is a special manifestation of the tendon reflexes of the digits), the fanning sign of Babinski and involuntary forced grasping. I therefore think that the pure pyramidal tract signs are relatively few, and they are associated with a flaccid paralysis, whereas in the presence of spasticity there is definite evidence that the premotor extrapyramidal projection systems are also involved. This allows the inference that the premotor area is essentially a region of the cortex which governs postural adjustments.

DR. HAROLD G. WOLFF, New York: Were the basal ganglia actually destroyed in any experiments, and if so what effect had this on the stimulation of area 6? It seems to me a little dangerous to infer from the action of the barbiturates in these experiments that there are any synapses lower down, that is, in the region of the basal ganglia. In my experiments with conditioned reflexes, the barbiturates caused a loss of conditioned responses before there was any perceptible change in motility and certainly long before there was any change in the unconditioned responses.

DR. S. W. RANSON, Chicago: Was the exploration carried downward to the cortex ventral to the motor area for the head region? It is possible to excite rhythmic masticatory movements from this most ventral part of the premotor cortex. Were these rhythmic masticatory movements seen?

In the cat it is easy to demonstrate them from the region just dorsal to the rhinal fissure and rostral to the presylvian fissure. They have been seen also in the monkey, and they have been obtained in man from area 6b.

With regard to the interruption of the pathway from the premotor region, the fibers which mediate the masticatory rhythmic response in the cat are not interrupted between the cortex and the motor nucleus of the fifth nerve. I have been able to trace that path with the Horsley-Clarke machine all the way from the cortex down, and it is not interrupted, as has been generally assumed, in the substantia nigra.

DR. PAUL C. BUCY, Chicago: In answer to Dr. Wolff, we have not destroyed the basal ganglia in any of our animals.

In answer to Dr. Ranson, we have explored that portion of the premotor cortex which is anterior to the face area of area 4, but I did not want to introduce that, as I was limiting my discussion purely to the extremities. Rhythmic movements of mastication have been elicited from it. In addition, anterior to that portion of area 6 which gives rise to movements in the extremities one can obtain movements of the head and eyes, which consist of rotation to the opposite side.

As to the pathway which conducts the impulses responsible for these movements, from the premotor cortex to the spinal cord, we have as yet no definite data, but investigation from a microscopic standpoint is now going forward.

PERICAPILLARY ENCEPHALORRHAGIA DUE TO ARSPHENAMINE

SO-CALLED ARSPHENAMINE ENCEPHALITIS

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AND

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NEW YORK

Within the last three years two cases of so-called arsphenamine encephalitis came under our observation. The first case was one of syphilis with a history of a recent infection, while in the second case the patient was known definitely to be nonsyphilitic, the clinical diagnosis resting between acute multiple sclerosis [1] and disseminated meningo-encephalomyelitis.[2] In addition to the significance of case 2 in that it is the second verified [3] instance of death caused by hemorrhagic encephalitis following the administration of arsphenamine in a nonsyphilitic patient,[4] our attention was drawn to the striking character of the lesion found at postmortem examination. The similarity of the terminal lesion in the two cases engrafted on a basic pathologic process, decidedly dissimilar in the two instances, demanded thorough investigation and evaluation, which led us to this study, in the course of which several questions were raised:

1. Is the term "arsphenamine encephalitis" justified in the absence of frankly inflammatory lesions and in the presence of a purely vascular alteration in the central nervous system?

From the Division of the Laboratories and Neurological Service of the Mount Sinai Hospital.

Read at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 10, 1933.

1. Strauss, I.: Acute Multiple Sclerosis, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 1125.

2. Strauss, I.; Rabiner, A., and Ginsburg, S. W.: The Clinical, Bacteriological and Epidemiological Aspects of Encephalomyelitis, Proc. A. Research Nerv. & Ment. Dis. **12**:262, 1932.

3. A third case, which presented a fairly definite clinical picture of arsphenamine encephalitis but in which there was no anatomic confirmation, was reported by J. R. Phelps (Reactions Incidental to the Administration of 194,778 Doses of Neoarsphenamine and Other Arsenical Compounds in the United States Navy, U. S. Nav. M. Bull. **27**:1, 1928).

4. Henneberg, R.: Ueber Salvarsan Hirntod, Klin. Wchnschr. **1**:207, 1922.

2. Is arsphenamine directly responsible for the injury to the vessels, causing hemorrhages, or does some process in the nature of a Herxheimer reaction provoke the anatomic manifestations of the disease?

3. Are protective means available to ward off the development of the condition which led to the fatal issue?

4. Does an analysis of the clinical manifestations yield a symptom complex enabling one to diagnose the condition without a precise knowledge of the precipitating cause, for example, the drug employed in our cases?

To find an answer to these questions we searched the literature in an attempt to supplement the study of the anatomic and clinical features of the two cases reported here with the observations in reported cases, as well as with the views held with regard to the incidence and the etiologic and other factors.

REPORT OF CASES

CASE 1.—*Pericapillary encephalorrhagia following administration of neoarsphenamine; fatal issue; necropsy.*

History.—B. G., a woman, aged 25, was admitted to the Mount Sinai Hospital on Dec. 5, 1929, in deep coma. Her mother was unable to give reliable data beyond the fact that, as far as she knew, the patient had never been seriously sick until the onset of the present illness, and that on the day preceding admission, at about 7 p. m., the patient told her that she was going to a physician to be treated for a "cold." When she returned a half hour later, she was pale and extremely nauseated. She vomited repeatedly that night and complained of severe headache. She remained in bed. On the next day the headache became more persistent and she vomited several times. At 4 p. m. of that day (the day of admission) she suddenly became irrational and appeared to suffer from more severe headache. Soon afterward she had a generalized convulsion and passed into deep coma. It was subsequently learned from the physician that he had treated her for a primary syphilitic lesion of the vagina several months previously, and that several days previous to the onset of the recent illness she had received a second or third injection of arsphenamine.

Examination.—The patient was in deep coma. There were gross nystagmoid movements of the eyes; left central facial paralysis, with deviation of the tongue to the left; hyperactive deep reflexes (the left greater than the right); transient bilateral ankle clonus; absence of abdominal reflexes, and submaxillary and mandibular adenopathy. There was no albumin, sugar or microscopic change in the urine. The Wassermann test of the blood was 4 plus. The cerebrospinal fluid was clear and contained 3 cells; the colloidal gold curve was 01122321000, and the Wassermann tests read as follows: 0.1 to 0.2 cc., negative; 0.4 to 0.6 cc., 3 plus; 0.8 to 1 cc., 4 plus.

Course.—On the day of admission the patient had another generalized convulsion, which was ushered in by a jacksonian seizure. It began with twitchings of the fingers of the left hand and spread rapidly to involve the entire body. Despite active therapy, including the intravenous administration of sodium thiosulphate, following a brief period of apparent improvement she declined rapidly. She died on December 7, two days after admission.

Necropsy.—Gross Anatomy: The brain was voluminous and showed moderate flattening of the convolutions. The pial vessels were markedly congested. The orbital surface of the right hemisphere showed marked discoloration owing to the subpial extravasation of blood. On sectioning, the most striking alteration was seen in the optic thalami, the centers of which were occupied by areas of discoloration due to diffusion of extravasated blood. Similar areas of discoloration were noted in the cornu ammonis, in the tegmentum of the midbrain (fig. 1) and in several areas of the pons and of the cerebellar cortex.

Microscopic Anatomy: Sections from the several hemorrhagic areas that came into view on gross section of the brain displayed a characteristic microscopic

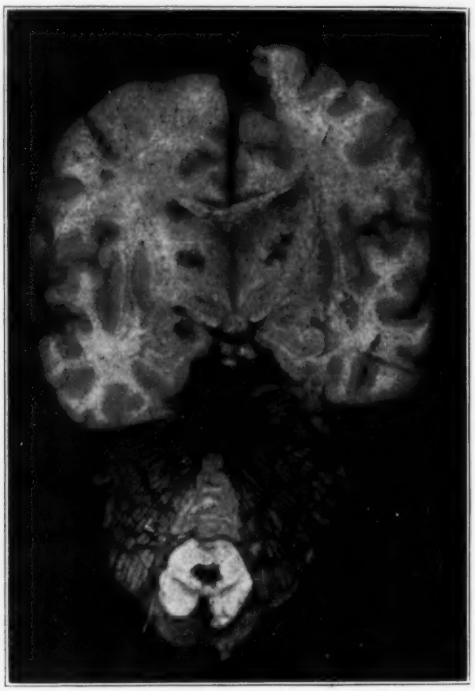

Fig. 1 (case 1).—Gross appearance and location of the conglomerate hemorrhages in the cerebrum and midbrain.

appearance (fig. 2). What seemed to the naked eye a solid mass of extravasation was readily recognized under moderate magnification as a conglomeration of numerous perivascular hemorrhages of the type usually described under the term of ring hemorrhages. The latter presented a clear, perhaps better described as an unstained, center, surrounded by a dense ring of extravasated blood (fig. 3). In the direct proximity of such conglomerates of ring hemorrhages there was found fairly constantly a larger vessel with an apparently intact wall, free from the hemorrhagic coat (fig. 4). A closer study of the clear centers, which were enveloped by the extravasated blood, revealed a central vessel; at times, it was also possible to discern smaller branches, radiating from the central vessel toward the periphery, where these vascular twigs were lost in the mass of extravasated

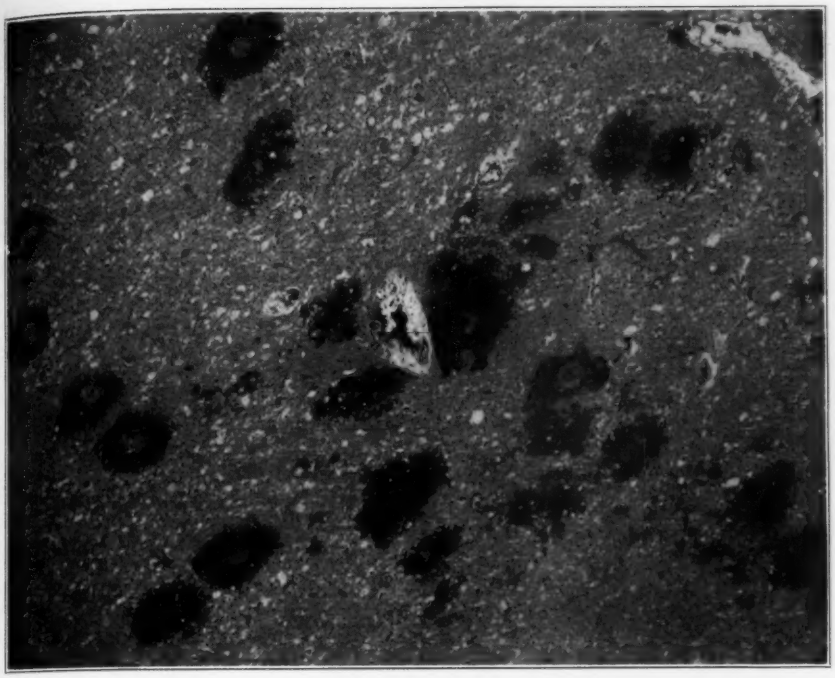

Fig. 2 (case 1).—Microscopic appearance of a conglomerate hemorrhage. It is apparent that what appears to the naked eye as a massive hemorrhage is in reality a collection of numerous pericapillary extravasations. Hematoxylin-eosin; × 46.

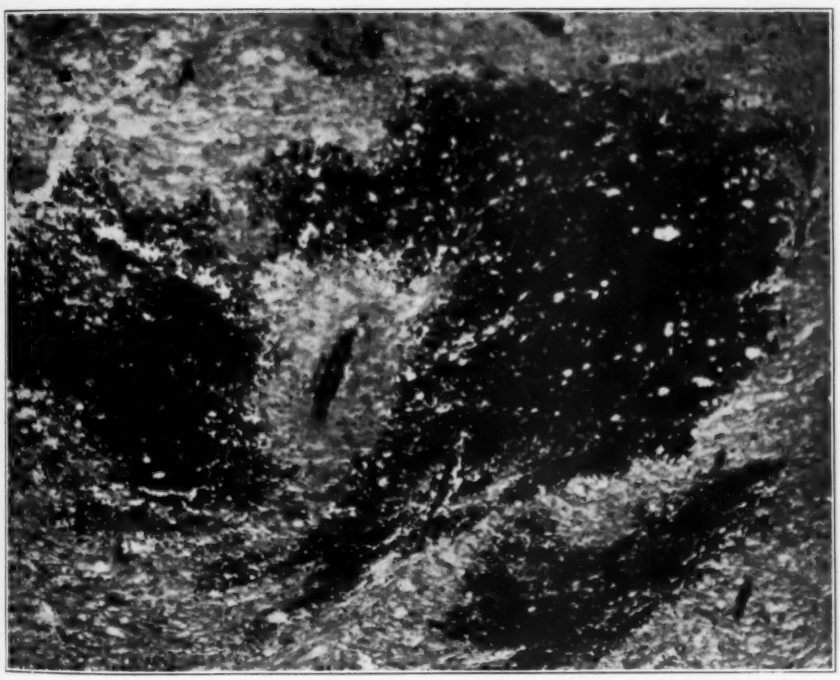

Fig. 3 (case 1).—An isolated ring hemorrhage. Hematoxylin-eosin; × 64.

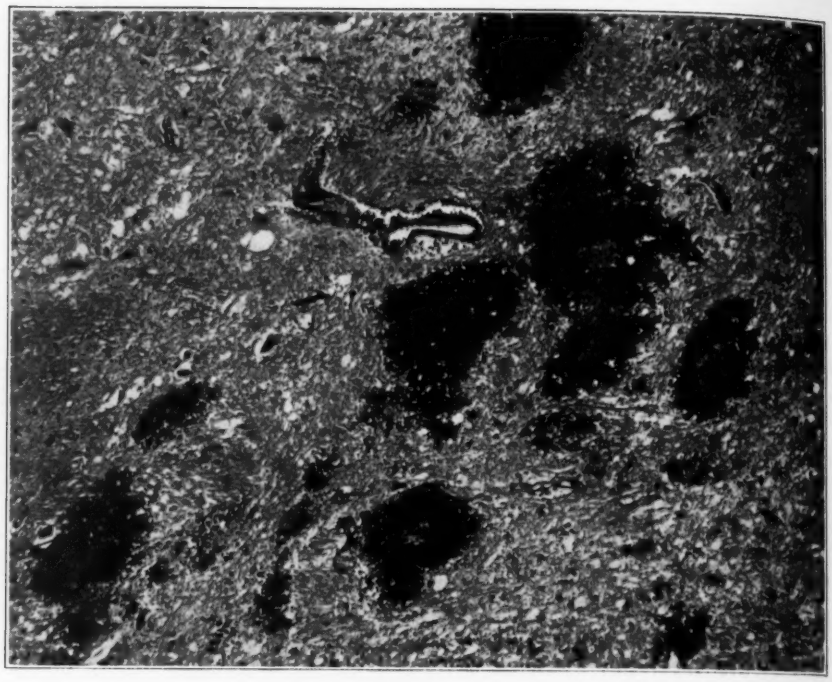

Fig. 4 (case 1).—A number of pericapillary hemorrhages alongside of an arteriole showing a few red blood cells in the perivascular territory. Hematoxylin-eosin; × 70.

Fig. 5 (case 1).—A ring hemorrhage showing a central vessel partially intact, with radiating capillaries extending into the hemorrhagic mantle. Globus' modification of the Hortega silver carbonate stain; × 450.

blood (fig. 5). Occasionally, when a favorable section was obtained at a critical point, a small capillary arising from an intact precapillary could be traced to its termination in a hemorrhagic ring (fig. 6).

With this fragmentary evidence, in the light of knowledge of the normal arrangement of blood vessels in the brain the reconstruction of the probable morphologic factors involved in the production of the so-called ring hemorrhages was not difficult. Thus, by selecting a cross-section at some critical point in the vascular tree in the brain substance (figs. 7 and 8), the relation of the precapillaries to their branchings could be readily seen. It revealed that a cross-section at a selected point shows a larger radical in the center, with smaller branches, capil-

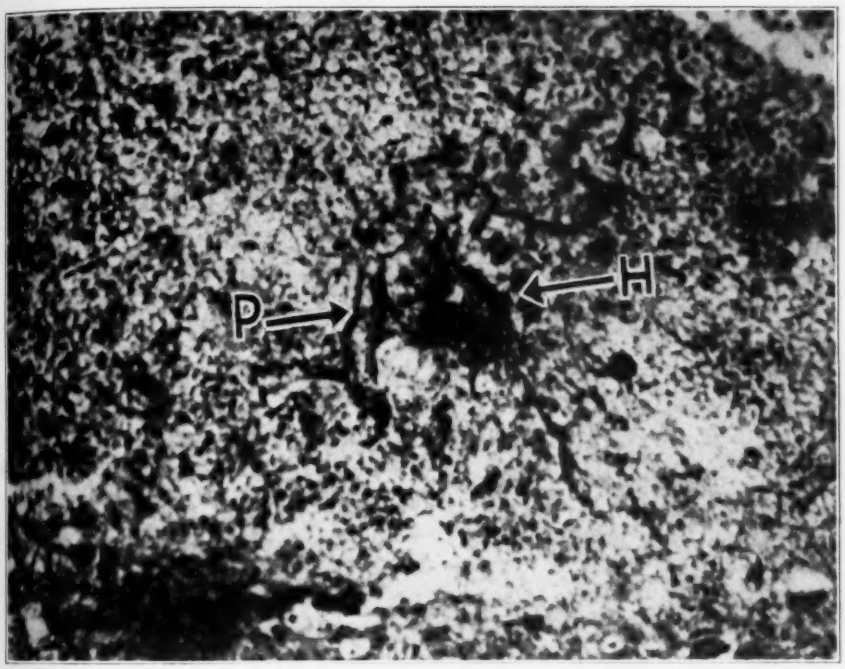

Fig. 6 (case 1).—A pericapillary (*P*) with a small branch terminating in a minute hemorrhage (*H*). Globus' modification of the Hortega silver carbonate stain; × 400.

laries, arranged in a circle around it. Hence, with a given precapillary in the center and its several branches arranged in a circle around it, when the latter undergo disruption the resultant hemorrhage, it may be assumed, will tend to assume the character of a circle at some distance from the central precapillary. In this way a clear zone is left directly around the central vessel, which in turn is surrounded by a dense hemorrhagic belt, with the result that the so-called ring hemorrhage is formed (fig. 9).

However, it would be fallacious to think that ring hemorrhages are specific for arsphenamine encephalorrhagia. Though in this disease the hemorrhages assume the ring form, this form may occur also in hemorrhagic lesions of the brain of different etiology. Thus they are encountered in the vicinity of tumors and in

direct proximity to inflammatory lesions. But there they are not predominant and are found alongside of more numerous solid extravasations (fig. 10). In such material it is possible to demonstrate that the difference between ring hemorrhages

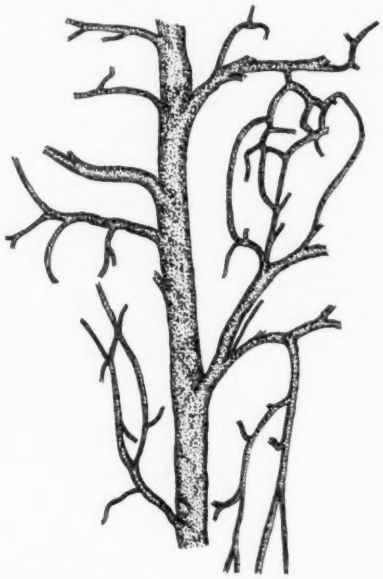

Fig. 7 (case 1).—A reconstructed vascular tree in the brain substance (after Pfeiffer: Anastomosen der Hirngefässe, J. f. Psychol. u. Neurol. **42**:1, 1931).

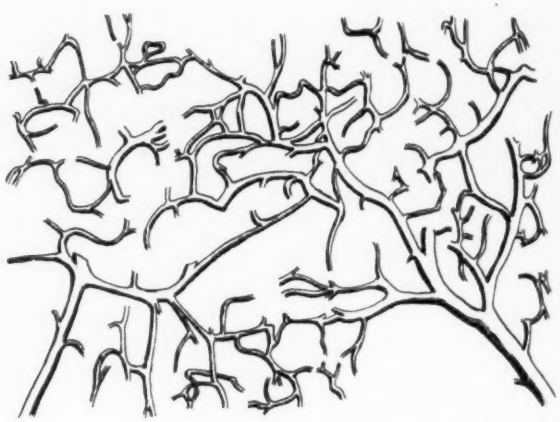

Fig. 8 (case 1).—Reconstruction of a vascular branching in the brain substance (after Pfeiffer: Anastomosen der Hirngefässe, J. f. Psychol. u. Neurol. **42**:1, 1931).

and the larger, solid hemorrhages is accounted for by the caliber of the vessel involved. When a number of small capillaries are the points of escape of blood,

a ring hemorrhage is produced, but when a larger radicle is involved central to the origin of the capillaries a more solid perivascular hemorrhage results (fig. 10).

While the ring hemorrhages constituted the main cerebral lesions in this case, changes of another type were also noted in the extravascular territory of the

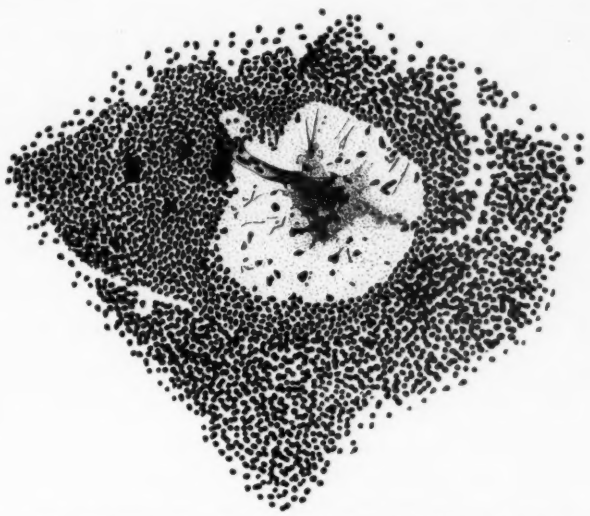

Fig. 9 (case 1).—A drawing of a ring hemorrhage.

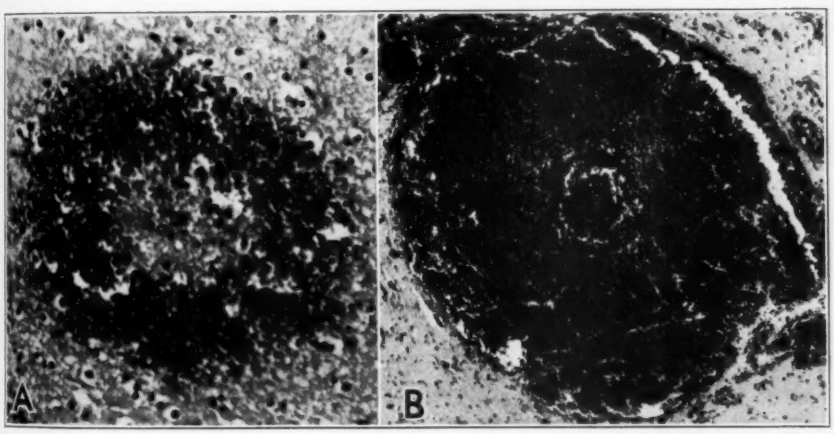

Fig. 10.—A ring hemorrhage alongside of a ball hemorrhage. Hematoxylin and eosin; *A*, × 200; *B*, × 65.

brain. They were mainly in the nature of reactive glial proliferation, provoked by the spread of the toxic substance. Since the vascularization of the brain is rather dense, it is readily realized that no part of the brain will completely escape injury. It is also patent that the reactive phenomena are most pronounced where the injury to the vessels is most pronounced. Thus, in the direct proximity of the more

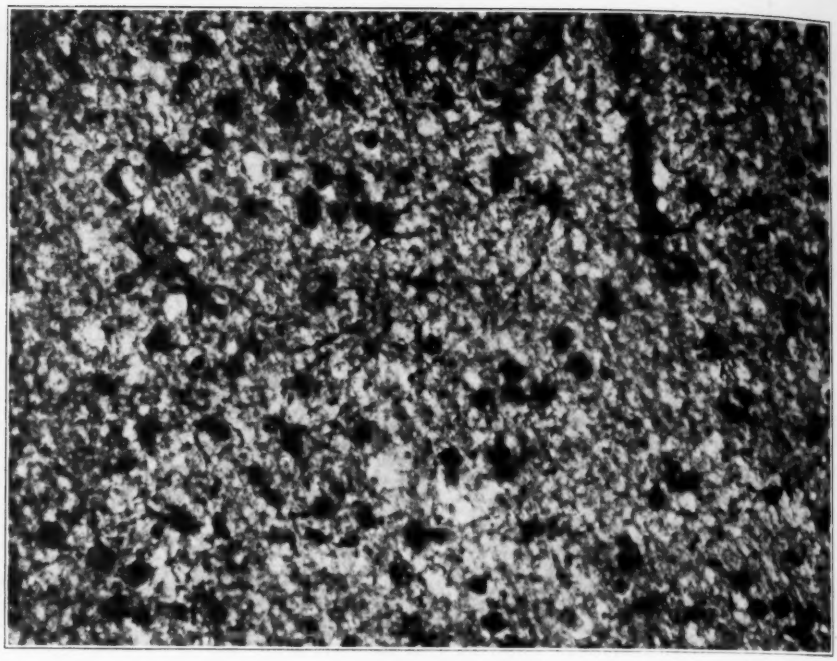

Fig. 11 (case 1).—Gliosis in the proximity of vascular damage. Globus' modification of the Cajal gold sublimate stain; × 400.

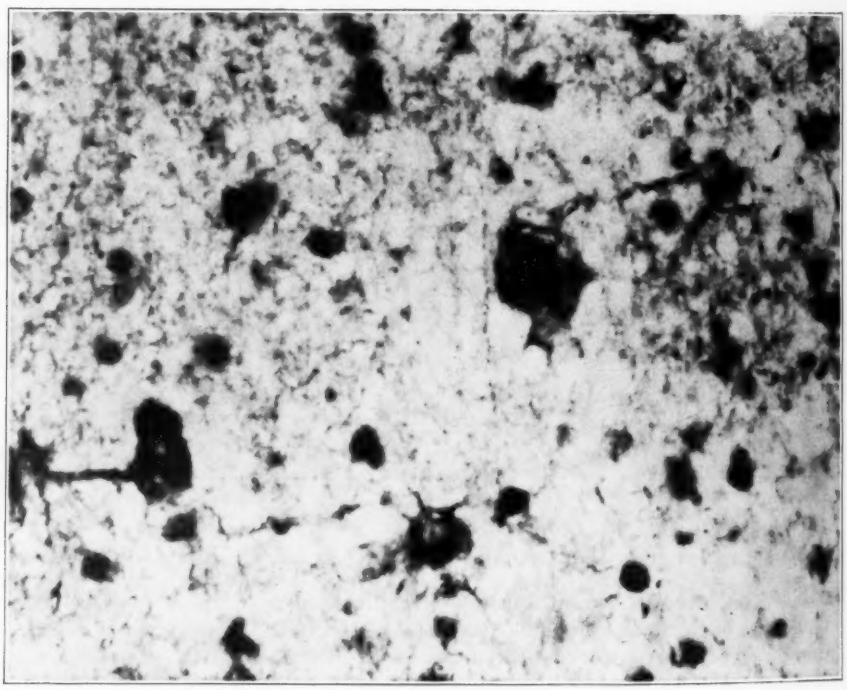

Fig. 12 (case 1).—Oligodendroglia, swollen and undergoing degeneration in areas somewhat remote from vascular damage. Globus' modification of the Hortega silver carbonate stain; × 700.

severely injured blood vessels more advanced gliosis had taken place (fig. 11), together with an increase in astrocytes and oligodendroglia (fig. 12). A few vessels revealed the picture of diapedesis.

Comment.—The lesions described in this case were mainly perivascular hemorrhages due to rupture of the smaller capillaries, moderate reactive gliosis in response to the toxic substance which had oozed through the injured vessel wall and diapedesis, which was an earlier stage in the process of extravasation.

CASE 2.—*Pericapillary encephalorrhagia following administration of arsphenamine in a case of disseminated sclerosis; fatal issue; necropsy.*[5]

History.—F. L., a woman, aged 40, married, was admitted to the Mount Sinai Hospital on Oct. 3, 1931, as a private patient of Dr. I. Strauss. One year previously, following a nervous shock, she complained of headache. Physical examination at that time gave negative results. She improved while under the care of the family physician, but six months later suddenly began to experience numbness of the left leg. A tingling sensation appeared in the left hand. She also noticed that the legs were weaker. About this time the headache reappeared. Neurologic examination disclosed: (1) retrobulbar neuritis, with central scotoma; (2) diminished deep reflexes on the left side, and (3) irregularly distributed sensory changes (hypalgesia, hypesthesia) with loss of vibratory sense in the right foot. Lumbar puncture yielded clear cerebrospinal fluid containing 14 cells per cubic millimeter (12 lymphocytes and 2 polymorphonuclear leukocytes). The total protein was 34 mg. per hundred cubic centimeters. The Wassermann and colloidal gold reactions were negative.

A course of nonspecific protein therapy was given, but the patient improved only slightly. It was then decided to administer an arsenical preparation. The patient received two injections of sulpharsphenamine (0.3 Gm.). Following the first injection there was improvement, but shortly after the second injection the patient began to complain of intense headache and bodily pain. On the same evening she became restless and confused, passed into semistupor and had three generalized convulsions.

Examination.—The patient was in semistupor and cyanotic and breathed with Cheyne-Stokes respiration. There was a maculopapular eruption over the entire body. Lumbar puncture yielded clear cerebrospinal fluid under normal pressure. The urine showed a large amount of albumin, pus, a strongly positive guaiac test for blood and a few granular casts.

Course.—Sodium thiosulphate was administered. The patient remained in stupor and died on the following day.

Necropsy.—Gross Anatomy: The pial vessels were moderately injected, giving the surface of the brain a congested and edematous appearance. On the lateral surface of the left temporal lobe there were several sharply circumscribed, grayish-red foci, marking areas of subarachnoid or subpial hemorrhage. On sectioning the brain there was found a larger number of similar sharply demarcated hemorrhagic foci. They were of variable size, some of them measuring about 1 cm. in diameter, and had the appearance of confluent, punctate hemorrhages. In the brain stem they had a bilaterally symmetrical location, while in the cerebral hemisphere they were irregularly disseminated. They were most conspicuous in the temporal

5. Dr. I. Strauss permitted us to report this case.

lobes, in the region of the internal capsule, the lenticular nuclei, the superior quadrigeminate bodies and the red nuclei and in the pons. A few were found in the medulla and in the spinal cord. None was found in the cerebellum.

In addition to the hemorrhagic foci, there were many sclerotic areas, which were fairly well demarcated and easily recognized by their pearly-white appearance. They were sharply delimited and irregularly disseminated throughout the cerebrospinal axis. They were more numerous in the spinal cord, where they had the characteristic appearance of disseminated sclerosis.

Microscopic Anatomy: Histologic examination of the hemorrhagic areas in the brain disclosed lesions (fig. 13) similar to those in case 1. They were char-

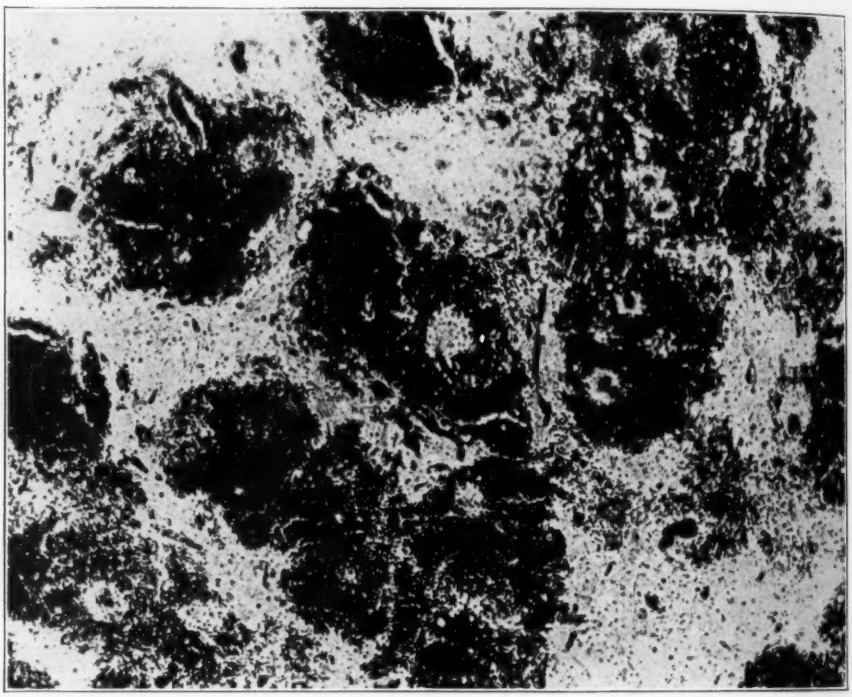

Fig. 13 (case 2).—Pericapillary hemorrhage of the ring variety. Globus' modification of the Hortega silver carbonate stain; × 35.

acterized by numerous ring hemorrhages, which to the naked eye gave the appearance of a solid and massive extravasation of blood.

The sclerotic patches presented histologic alterations typical of multiple sclerosis (fig. 14). Under a higher magnification, the sharp demarcation of the sclerotic area from the uninvolved area was well brought out in Spielmeyer's preparations. This was also well shown in sections of spinal cord cut in the long axis (fig. 15). These sclerotic areas, when studied by means of special silver stains, disclosed complete dissolution of myelin as well as marked destruction of axis-cylinders (fig. 16*A*). But a few naked axis-cylinders were left intact, and the glial elements were numerous. In preparations stained with scarlet red the glial elements were shown to be mainly compound granular cells (scavenger cells) loaded with fat

Fig. 14 (case 2).—Section of the medulla oblongata, at the decussation of the pyramids, showing fusion of several sclerotic patches in the marginal and intermediate zones of the dorsal and lateral columns. Spielmeyer myelin stain; × 7.

Fig. 15 (case 2).—Longitudinal sections of the spinal cord, showing fusion of several sclerotic patches. Spielmeyer's myelin stain; × 46.

(fig. 16 *B*). These cells appear in the photomicrograph as black-stained bodies, of irregular outline, some of which demonstrate the granular character.

A search for manifestations of an inflammatory lesion revealed no evidence of lymphocytic infiltration either of the frank inflammatory or of the reactive type, and only an occasional glial nodule was found in the gray matter outside of the frank sclerotic patches.

Comment.—From the description given it is obvious that this case was one of the acute form of disseminated sclerosis [1] involving the cerebrospinal axis in the typical disseminated fashion. The sclerotic areas

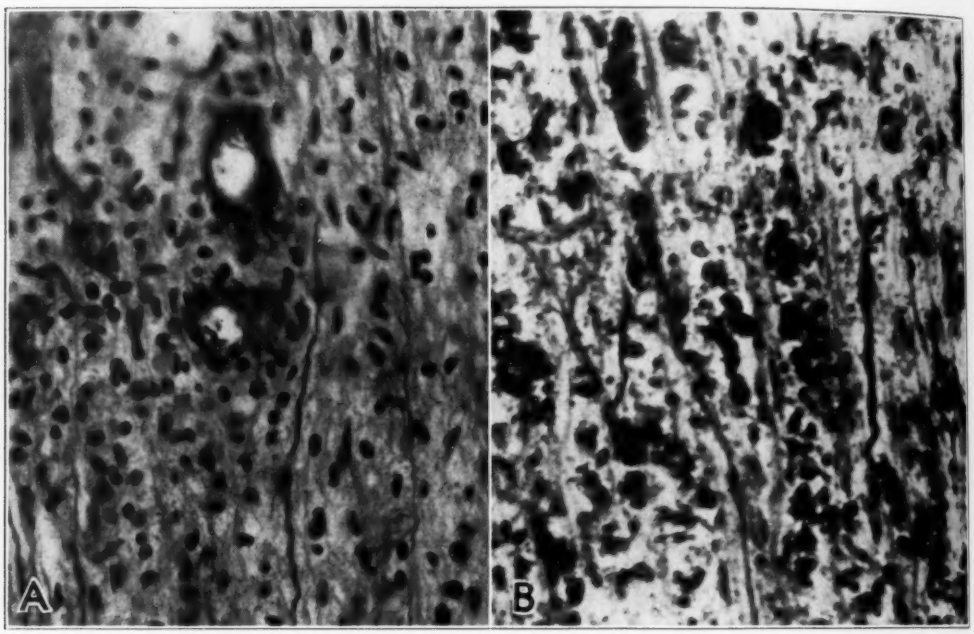

Fig. 16 (case 2).—*A*, longitudinal section of the spinal cord, showing a few naked axis-cylinders in a sclerotic patch. The dark-staining spheres are nuclei of the compound granular cells, which in *B* are brought out by the fat stain. Bielschowsky's silver method; × 200. *B*, a section similar to that shown in *A*, counterstained with scarlet red to illustrate the large number of compound granular cells loaded with fat. In the reproduction the red granules appear black. Magnification, × 460.

presented only degenerative alterations, such as demyelinization, destruction of axis-cylinders and massive accumulation of compound granular cells. The absence of inflammatory lesions excluded even the remote possibility of a syphilitic process. The hemorrhagic lesions were identical with those described in case 1 and bore no relationship to the underlying disease, which was typical of so-called acute multiple sclerosis. The

hemorrhagic lesions were unquestionably provoked by the sulpharsphenamine.

The data assembled in the course of a survey of the literature with reference to so-called arsphenamine encephalitis are expressed mainly in figures; hence, they will be presented in the main in the form of tables.

INCIDENCE OF DEATHS ATTRIBUTED TO ARSPHENAMINES

The relative incidence of deaths following the administration of arsphenamines as reported from various reliable sources is recorded in table 1. It will be seen that, despite the large number of injections given, fatalities are relatively few. It is, however, difficult to obtain an accurate estimate of the relative number of deaths due to hemorrhagic encephalitis if confirmation of the clinical diagnosis by postmortem findings is demanded. It is commonly agreed that the number of fatal issues caused by involvement of the central nervous system represents

TABLE 1.—*Incidence of Deaths Attributed to Arsphenamines*

Series	Cases	Total Number of Doses Administered	Deaths
United States Navy	.....	272,354	17
British Research Council			
Hospital A	1,629	13,000	1
Hospital B	375	.....	1
Hospital C	9,758	.....	26
Civil statistics (extramural)	77,645	298,011	10
Cologne	.....	225,780	12
Cleveland	.....	78,350	12

about one half of the total number of deaths. For instance, in the series reported by Phelps and Washburn,[6] of the United States Navy, covering ten years, there were thirty-four deaths following the administration of arsphenamine, twenty of which were attributed to encephalitis. In the series reported by Cole and his associates[7] from the Cleveland Clinics, six of the twelve deaths were thought to have been due to hemorrhagic encephalitis. However, it is apparent that so striking a symptom complex as arsphenamine encephalitis probably finds its way into literature in disproportionate numbers.

A careful search of the literature for authentic cases in which postmortem examination confirmed the clinical diagnosis of hemorrhagic encephalitis yielded only sixty cases. Fourteen other cases without sig-

6. Phelps, J. R., and Washburn, W. A.: Toxic Effects of Arsenical Compounds Employed in the Treatment of Syphilis in the United States Navy, U. S. Nav. M. Bull. **28**:659, 1930; Urol. & Cutan. Rev. **34**:458, 1930.

7. Cole, H. N.; DeWolf, H.; McCuskey, J. M.; Miskjian, H. G.; Williamson, G. S.; Rauschkolb, J. R.; Ruch, R. O., and Clark, T.: Toxic Effects Following Use of Arsphenamines, J. A. M. A. **97**:897 (Sept. 26) 1931.

nificant postmortem findings but presenting the typical clinical picture may be added to the total.[8]

Type of Arsphenamine Used in Fatal Cases.—In general, no single preparation is to be indicted as playing a determining rôle in the

8. Assmann, H.: Berl. klin. Wchnschr. **49**:2346, 1912. Almkvist, J.: München. med. Wchnschr. **58**:1809, 1911; in Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1911, vol. 2, p. 443. Balzar, M. F., and Coudat, R.: Bull. Soc. franç. de dermat. et syph. **23**:48, 1912. Blanton, W. B.: Am. J. Syph. **3**:648, 1919. Busse, O., and Merian, L.: München. med. Wchnschr. **59**:2330, 1912; in Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1913, vol. 3, p. 534. Caesar, V.: Dermat. Ztschr. **20**:569, 1913. Ceelen: Berl. klin. Wchnschr. **58**:1195, 1921. Cummer, C. L.: Ohio State M. J. **27**:117, 1931. Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1912, vol. 2, pp. 547 and 568; 1913, vol. 3, p. 545; Correspondence, Brit. M. J. **1**:1044, 1914. Fahr, T., and Hahn, R.: München. med. Wchnschr. **67**:1222, 1920. de Favento, P.: Gior. ital. di mal. ven. **53**:177, 1912. Fischer, B.: München. med. Wchnschr. **58**:1803, 1911; in Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1912, vol. 2, p. 424. Fritz, E.: Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:163, 1930. Gammeltoft, S. A.: Acta obst. et gynec. Scandinav. **9**:167, 1930. Gjessing, H. C.: Acta dermat.-venereol. **8**:268, 1928. Hammer, F., in Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1913, vol. 3, p. 351. Henneberg, R.: Klin. Wchnschr. **1**:207, 1922. Hirsch, F., in Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1913, vol. 3, p. 347. Kanengieser: München. med. Wchnschr. **58**:1806, 1911; in Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1912, vol. 2, p. 435. Kerl, W.: Wien. klin. Wchnschr. **29**:1227, 1916; in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 18, p. 604. Klieneberger, C.: Deutsche med. Wchnschr. **38**:1691, 1912. Lube, F.: Dermat. Ztschr. **20**:8, 1913. Lissauer, M.: Deutsche med. Wchnschr. **43**:1471, 1917. von Marschalko, T., and Vespremi: Arch. f. Dermat. u. Syph. **112**:813, 1912; **114**:589, 1912. Martin, L.; Darre, H., and Gery, L.: Bull. et mém. Soc. méd. d. hôp. de Paris **37**:215, 1914. Meirowsky, E., and Kretzmer: Prakt. Ergebn. a. d. Geb. d. Haut- u. Geschlechtskr. **3**:444, 1914. Miller, M. K.: Four Types of Encephalitis, J. A. M. A. **97**:161 (July 18) 1931. Parnell, R. J. G., and Dudley, S. F.: Lancet **1**:190, 1920. Phelps, J. R., and Washburn, W. A.: U. S. Nav. M. Bull. **28**:659, 1930; Urol. & Cutan. Rev. **34**:458, 1930. Pines, L., and Prigonikow, J.: Arch. f. Psychiat. **90**:185, 1930. Pinkus, F.: Dermat. Wchnschr. **19**:675, 1912. Pollak, E., and Riehl, G.: Jahrb. f. Psychiat. u. Neurol. **47**:99, 1930. Post, C. D.: Am. J. Syph. **11**:444, 1927. Ravaut, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **32**:365, 1911; Rouget, M.: ibid. **32**:621, 1911. Scott, E., and Moore, R. A.: J. Lab. & Clin. Med. **13**:345, 1928; Am. J. Syph. **12**:252, 1928. Sée, M.: Ann. d. mal. vén. **14**:341, 1919. Tomascewski, E.: Dermat. Ztschr. **20**:283, 1913. Toxic Effects Following Use of Arsenobenzol Preparations, Medical Research Council, Special Report Series, no. 66, London, His Majesty's Stationery Office, 1922. Treupel, G.: Deutsche med. Wchnschr. **37**:1012, 1911. Phelps, J. R.: U. S. Nav. M. Bull. **22**:217, 1925. Wood, C. J.: ibid. **27**:508, 1929. A Fatal Case of Acute Poisoning by Neoarsphenamine, Reported as "Encephalitis," ibid. **27**:778, 1929. Wood, A. E. B.: J. Roy. Army M. Corps **24**:272, 1915. von Zumbusch: München. med. Wchnschr. **63**:750, 1916.

causation of deaths following its use (table 2). The drugs most frequently used are responsible for the greater number of deaths. Cole's [7] series is the only exception; it seems to corroborate the current clinical impression that sulpharsphenamine is highly toxic and involves risks out of proportion to its supposedly greater efficiency. A recent survey by the Council on Pharmacy and Chemistry of the American Medical Association [9] revealed that many experienced syphilologists have given up the use of sulpharsphenamine.

TABLE 2.—*Type of Arsphenamine Used in Fatal Cases*

	Collected Cases	Navy, 1928	Cole, 1932
Neoarsphenamine	16	16	1
Arsphenamine	18	1	1
Sulpharsphenamine	3	0	4
Myosalvarsan	2	..	..
Novarsenobillon	2	..	..
Sodium arsphenamine	1	..	..

TABLE 3.—*Distribution of Fatal Cases as to Sex and Age*

Sex			Age in Years		
Male	Female	Unrecorded	Average	Minimum	Maximum
24	18	6	25⅝	2	41

TABLE 4.—*Number of Injections Which Preceded the Onset of Grave Symptoms*

Injections	Collected Cases	Navy	Cole
1	6	1	..
2	15	10	1
3	12	2	3
4	4	..	1
5	..	1	..
8	1	2	..
9	..	..	1
Many	4	..	1

Distribution of Fatal Cases as to Sex and Age.—Early adult life is the period of greatest incidence, but this is conditioned by other factors, such as the greater frequency of the early stages of syphilis in that age period (table 3).

Number of Injections Which Preceded the Onset of Grave Symptoms.—It is commonly said that the first or second injection of an arsphenamine preparation is the most critical in precipitating the events causing a fatal issue. This is borne out by table 4, which shows that the relatively greatest number of deaths reported followed the second

9. Sulpharsphenamine, Its Uses and Limitations, Report of the Council on Pharmacy and Chemistry of the American Medical Association, J. A. M. A. **99:** 1688 (Nov. 12) 1932.

injection of arsphenamine. However, it is equally true, as this table shows, that a fatal issue may occur at any stage of arsphenamine therapy.

Time Elapsing Between Injection and (a) the Onset of Frank Symptoms of Encephalitis and (b) Death.—The time element in treatment with arsphenamine was also considered, and some information was

TABLE 5.—*Time Elapsing Between Injection and Onset of Frank Symptoms of Encephalitis*

Average	2½ days
Minimum	2 hours
Maximum	42 days
In most cases from 2 to 3 days	

TABLE 6.—*Time Elapsing Between Injection and Death*

Average	3.1 days
Minimum	2 hours
Maximum	7 weeks

TABLE 7.—*Heavy Metal Preparations Used in Initial Stage of Treatment*

Metal	Cases
Mercury	41
Bismuth	2
No mercury	11

TABLE 8.—*Type of Syphilis* *

	Cases
Primary	19
Secondary	13
Tertiary	10

* No stage immune.

obtained as to the latent period between the administration of the drug and the provocation of signs of arsphenamine encephalitis (tables 5 and 6).

The Type and Effect of Heavy Metal Preparation Used in the Initial Stage of Treatment.—It is also said that it is advisable, if not essential, as a protective measure to precede the arsphenamine therapy by an initial administration of a heavy metal preparation by the intramuscular route. This, however, is not borne out by table 7, which shows that in the greater number of fatal cases (forty-one) the patients had received a mercury or bismuth compound; only eleven had not been given a similar drug.

Forms of Syphilis and Their Participation in the Syndrome of Arsphenamine Encephalitis.—The activity and stage of the infection has often been brought into the discussion of the probable factors involved in the precipitation of the untoward reaction to arsphenamine. This influence is apparently negated by the data in table 8.

Symptoms and Signs of Arsphenamine Encephalitis.—It is desirable to obtain a clear picture of the clinical symptom complex characteristic of this disease, whereby the diagnosis can be made without the assistance of a history disclosing the administration of the drug. Hence all symptoms and signs incident to this disease have been tabulated in the order of their frequency (table 9). Little was found beyond an array of signs and symptoms which may be caused by any widespread disease of the central nervous system, whether degenerative or inflammatory in origin.

TABLE 9.—*Common Symptoms*

Symptoms	Cases
Stupor	42
Convulsions	37
Bloody cerebrospinal fluid	29
Vomiting	27
Headache	20
Fever	20
Dizziness	11
Delirium; excitement	14
Focal signs (in order of greater frequency)	
Reflex changes, including the Babinski sign	14
Loss of corneal reflex	6
Disturbance in speech	5
Tremors	5
Loss of light reflex	5
Hemiplegia	3
Nystagmus	2
Facial palsy	2
Quadriplegia	1
Palsy of the abducens nerve	1
Conjugate deviation	1

GENERAL COMMENT

The nervous system, when affected unfavorably by the administration of arsphenamine, apparently reacts to the drug in varying degrees which manifest themselves in a series of syndromes described under the following heads: (1) nitritoid crisis, so called because of its resemblance to the clinical picture produced by nitrates, which is characterized by general symptoms, such as syncope, blanching, vomiting, lowered blood pressure and alterations in pulse and respiration; (2) the Herxheimer reaction; (3) serous apoplexy (Milian [10]), a poorly defined clinical entity in which, it is thought, the underlying pathologic changes are marked edema and congestion of the brain; (4) hemorrhagic encephalitis.

It is not improbable that all of the conditions enumerated are purely quantitative variations of an essentially similar process, provoked by the

10. Milian, G.: Apoplexie séreuse arsénicale, Acta dermat.-venereol. **9**:149, 1928.

toxic effect of the drug employed. The nitritoid reactions, which were considered for some time to be anaphylactoid, are no longer considered so. As early as 1922, the British Medical Research Council [11] advocated the abolition of the term "anaphylactoid" as applied to reactions to arsphenamine, since they found no valid evidence to support such a conception. Indeed, the dilatation of the capillaries, common to nitritoid reactions, may be held responsible in some instances for the cerebral and meningeal congestion, which is but a milder degree of the vasomotor disturbance assumed to be the cause of so-called serous apoplexy. It may be equally true that in conditions in which extreme dilatation of smaller branches of the vascular apparatus results in hemorrhages this is little else than a more drastic form of the damage to the vessels. It may thus be assumed that the essential factor in the various reactions considered is the vascular injury. But it still is necessary to define the cause of such an injury—a problem which, despite an abundant literature on the subject, is yet to be solved. Ehrlich [12] was of the opinion that the damage to the nervous system could not be accounted for by a direct effect of the drug. He insisted that only acute yellow atrophy of the liver should be considered as due to the toxicity of the drug. He looked on the so-called encephalitic changes as an expression of a Herxheimer reaction, in which the drug, causing a massive destruction of spirochetes, liberates toxic bodies which are directly responsible for the pathologic changes in the brain. But when one considers that many of the reported deaths occurred in instances of primary syphilis at a time when spirochetes had not yet lodged in the brain substance and, moreover, that in many instances of secondary and tertiary syphilis autopsy disclosed no syphilitic lesions in the brain, it is difficult to accept this explanation. To meet these objections Pinkus [13] suggested the possibility that toxic bodies might have been liberated elsewhere in the organism and that, when transported by the blood stream to the brain, they provoked the manifestations of a Herxheimer reaction.

Other claims were made for the occurrence of a true Herxheimer reaction implicating the central nervous system, on the ground that deaths have also occurred in cases which lacked the picture of hemorrhagic encephalitis. Thus, Jakob [14] reported three cases which presented

11. Toxic Effects Following Use of Arsenobenzol Preparations, Medical Research Council, Special Report Series, no. 66, London, His Majesty's Stationery Office, 1922.

12. Ehrlich, P.: Abhandlungen ueber Salvarsan, Munich, J. F. Lehmann, 1912, vol. 2, pp. 547 and 568; 1913, vol. 13, p. 545.

13. Pinkus, F.: Zur Kenntnis der Hirnschwellungerscheinungen während der Syphilisbehandlung, Dermat. Wchnschr. **19**:675, 1912.

14. Jakob, A.: Ueber Hirnbefunde im Fällen von Salvarsantod, Ztschr. f. d. ges. Neurol. u. Psychiat. **19**:189, 1913.

frank syphilitic changes in the brain but did not reveal the picture of hemorrhagic encephalitis. But this contention fails to impress one in view of our case 2, that of a definitely nonsyphilitic patient in whom hemorrhagic encephalitis was established by necropsy.

Some authors who were disinclined to accept the Herxheimer reaction as the cause of the encephalitis hemorrhagica have offered other explanations for this phenomenon. Thus, Wechselmann [15] expressed the belief that an excessive retention of the drug, because of poor elimination, serves as the precipitating factor. He pointed to a concurrent damage of the kidney, which he incidentally attributed to the previous administration of a mercury preparation. But this is not borne out by either clinical or pathologic observations. First, a fair percentage of all patients so affected have not received preliminary treatment with mercury or bismuth compounds. Second, an even larger percentage did not reveal during life any changes in the urine which would warrant the assumption of the existence of renal disease. Third, in only about 10 per cent of cases were pathologic changes found in the kidneys post mortem. One fact, however, suggestive of the rôle played by renal insufficiency is the frequency of hemorrhagic encephalitis in pregnant women who have received arsphenamine during the period of gestation.

The view was also advanced that the vascular damage was due to a probable insufficiency of epinephrine, the hormone assumed to be necessary to counteract the dilating influence of arsphenamine. There is, however, no conclusive evidence to substantiate this supposition beyond the experimental studies of Brown and Pearce,[16] who found that in animals that received toxic doses of arsenical compounds the suprarenal glands revealed marked congestion, hemorrhage and necrosis. Tannenberg and Fischer,[17] among others, suggested that the assumed dysfunction of the cerebral vessels, resulting in hemorrhages, may have been caused by the action of the arsphenamine on the nerve terminal to the cerebral vessels. Here again there is no substantiating histologic evidence.

In final analysis, it seems to us that the most probable conception as to the pathogenesis of the condition in question is probably simpler.

15. Wechselmann, W.: Ueber die Pathogenese der Salvarsanschädigung, Berlin, Urban & Schwarzenberg, 1913; Reports of Salvarsan Fatalities, Urol. & Cutan. Rev. **17**:649, 1913; Ueber die Pathogenese der Salvarsantodesfälle der Schwangeren, München. med. Wchnschr. **64**:345, 1917. Wechselmann, W., and Bielschowsky, M.: Thrombose der Vena magna Galeni, Dermat. Wchnschr. **69**: 763, 1919.

16. Brown, W. H., and Pearce, L.: Pharmacological Action of Arsenicals on the Adrenals, J. Exper. Med. **22**:535, 1915.

17. Tannenberg, J., and Fischer, B.: Gefässnerven und lokale Kreislaufstörung, Frankfurt. Ztschr. f. Path. **33**:91, 1925.

It is not inconceivable that a direct and selective effect of the arsphenamine, or of some of its fractions, on the vascular endothelium is responsible for the disruption of the capillaries, resulting in hemorrhage. In support of this conception there are a number of corroborative observations: 1. It is known that arsphenamine may act as a vasodilator, and with a greater concentration of the drug in the smaller vessels, this pharmacodynamic property may enhance the action of the arsenic in its attack on the capillaries. 2. The clinical picture of arsphenamine encephalorrhagia is not unlike that in inorganic arsenic poisoning. 3. Changes in the brain similar to those noted in arsphenamine encephalorrhagia are known to occur in vascular damage provoked by a variety of dissimilar poisons, such as carbon monoxide, phosgene and mercury, or by other disrupting influences, such as the proximity of a tumor or of inflammatory processes.[18] 4. Recent investigations by de Asuna and Kuhn[19] showed that arsphenamine has a specific and selective action on the reticulo-endothelial structures. These observations are in accord with current views that the therapeutic action of arsphenamine occurs largely through the agency of the reticulo-endothelial cells. 5. The demonstrable pathologic changes in so-called arsphenamine encephalitis are such as to indicate a specific vascular damage to the endothelial lining of the vessels, leading to diapedesis and to more extensive extravasation in severer injury to the vessels. This is corroborated by the observations of von Marschalko[20] and others, who have been able to reproduce the endothelial damage, stasis and hemorrhage in animals by employing arsphenamine in appropriate dosage.

CONCLUSIONS

1. Two cases of death caused by arsphenamine are described, one of which occurred in a nonsyphilitic patient.

2. The clinical and etiologic aspects of this syndrome are reviewed.

3. The essential pathologic alterations, which are mainly pericapillary hemorrhages, are recorded. The nature of the so-called ring hemorrhages is discussed, and their morphologic peculiarities are explained on the basis of selective damage to the capillaries.

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18. Alpers, B. J.: So-Called "Brain Purpura" or "Hemorrhagic Encephalitis," Arch. Neurol. & Psychiat. **20**:497 (Sept.) 1928. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 389.

19. de Asuna, J., and Kuhn, M. J.: Salvarsan und Retikuloendotheliales System, Rev. Soc. argent. de biol. **4**:122, 203 and 595, 1928.

20. von Marschalko, T., and Vespremi: Experimentelle und histologische Studien ueber Salvarsanstod, Arch. f. Dermat. u. Syph. **112**:813, 1912; **114**:589, 1912.

4. In view of these changes in the brain, it is suggested that there is no justification for the use of such terms as "arsphenamine encephalitis" or "hemorrhagic encephalitis," and that the term "pericapillary encephalorrhagia due to arsphenamine" is more appropriate.

DISCUSSION

Dr. Arthur Weil, Chicago: On Feb. 15, 1931, Dr. N. K. Lazar, of the Department of Ophthalmology of Northwestern University, and I read before the Chicago Ophthalmological Society a paper, entitled "Experimental Lesion in Tryparsamide Poisoning in Rabbits." We injected gradually increasing amounts of tryparsamide, beginning with 0.5 Gm. and increasing to maximal doses of 1.5 Gm., and killed the animals after from three to six weeks. The histologic study showed pictures similar to those presented by Dr. Globus.

Therefore, one can well agree with Dr. Globus that the clinician should abandon the old conception of encephalitis haemorrhagica as he has abandoned, or should abandon, the conception of polioencephalitis haemorrhagica superior in alcohol intoxication.

Dr. Israel Strauss, New York: My remarks do not bear on the pathologic histologic changes, which Dr. Globus has so excellently demonstrated. I want to call attention, however, to the action of the drug in the second case. I reported this case in the Libman anniversary volume because of its interest in relation to the question of so-called acute multiple sclerosis. My associates and I had, at various times, in cases of multiple sclerosis used sulpharsphenamine instead of solution of potassium arsenite, with the idea that we could give a little more concentrated arsenic by that method. Sulpharsphenamine has been used a great deal in Germany and, under a different name, has been reported as not extremely toxic. We gave this woman 3 dg. intramuscularly. She had been doing extremely well. After that administration, she suffered from headache and had slight fever. The physician who administered the drug did not sense this reaction as being of any importance, and five days later he repeated the dose. Almost immediately thereafter, she became comatose, and she died with the symptoms that one associates with arsphenamine encephalitis.

Stokes, in this country, definitely stated that sulpharsphenamine is dangerous, and he no longer uses it in the treatment of syphilis.

THE MYTH OF THE OCCIPITOFRONTAL ASSOCIATION TRACT

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Immediately above and parallel to the superior edge of the caudate nucleus is a bundle of nerve fibers which has been a bone of contention among neurologists for the last fifty years. In the fixed human cerebrum this fiber bundle may be distinctly seen projecting into the body of the lateral ventricle for about 1 mm. It lies close to the undersurface of the corpus callosum, between it and the head and the body of the caudate nucleus. Covered with the ependyma, it has a glistening white appearance in the fixed brain and is tough to the touch. Its thickness from above downward is difficult to estimate for reasons which will appear later; it is, roughly, about 2 mm. thick. Its width is about one-half that of the internal capsule. Its length, from before backward, as it is seen in the body of the ventricle with the ependyma intact, is about 3 cm.

Although different writers have, for different reasons, called this bundle by different names, they all agree regarding its appearance as described in the preceding paragraph. There is, morever, almost general agreement regarding its forward course above and in front of the head of the caudate nucleus. There it ceases to be a compact bundle and forms a radiation in the frontal and prefrontal regions and perhaps in the anterior portion of the parietal lobe. The sharp and conflicting differences of opinion are centered mainly on the origin or destination of its posterior extremity.

The controversy had its beginning in a demonstration by Onufrowicz [1] of the brain of a microcephalic idiot who lived to be 37 years of age. Of the several commissures which connect the two hemispheres of the normal cerebrum the anterior was the only one present. There were absent, besides the olfactory bulbs, the entire convolution of the cingulum, the lyra, the soft commissure and other less prominent structures. The corpus callosum was represented by a membrane. The mesial surface of the hemisphere presented a radial arrangement of the convolutions. Above the caudate nucleus and parallel to it, in the place of the corpus callosum, was a sagitally placed band of fibers which spread out in front to the frontal lobes and was

Read at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 9, 1933.

1. Onufrowicz, W.: Das balkenlose Microcephalen-Gehirn, Arch. f. Psychiat. **18**:305, 1887.

apparently continued behind as the tapetum on the walls of the occipital and temporal horns of the lateral ventricle.

When received by Onufrowicz, the rare specimen had been carelessly treated and was in very poor condition. It was flattened, probably by pressure against the bottom of the container. It was found to be decomposing in the solution of potassium bichromate in which it had been placed, so that the investigator was compelled to put it in a solution of alcohol. The specimen was crumbling. The sections, as a result of imperfect fixation, would not stain, and Onufrowicz stated that it was impossible to study details. The important facts of which he was certain were that the corpus callosum was absent, and that the tapetum was intact and was continuous in front with the sagittal band of fibers which was placed above and parallel to the upper edge of the caudate nucleus and which, in front, radiated toward the frontal lobe. He therefore concluded that in the normal brain the tapetum is not a part of the corpus callosum, but is continuous with the posterior part of the sagittal bundle above the caudate nucleus, the whole constituting an occipitofrontal association system.

Forel,[2] under whose guidance the foregoing investigation was made, and who made most of the drawings for Onufrowicz and presented his paper, was thoroughly in accord with his conclusions.

Muratoff,[3] in an experimental study of secondary degeneration in dogs, found the occipitofrontal fasciculus to degenerate in part after ablation of the motor area. "Its inner and lower portions," he said, "the fibers which appertain to the corpus callosum and to the caudate nucleus, remained normal." He was not at all certain that the fasciculus in question was an occipitofrontal association system. He therefore preferred to call it "the fasciculus subcallosus."

Curiously, both Onufrowicz and Forel thought that the association system which in the normal cerebrum corresponds to the occipitofrontal fasciculus which they observed in the idiot's brain was the fasciculus arcuatus of Burdach. To this Dejerine[4] justly objected. He pointed to the fact that Burdach's fasciculus arcuatus is situated in the external capsule, lateral to the corona radiata, while the occipitofrontal fasciculus, or the fasciculus subcallosus of Muratoff, is placed mesial to the corona radiata. For the rest he thoroughly agreed with Onufrowicz and Forel

2. Forel, A.: Balkendefecte, in Gesammelte Hirnanatomische Abhandlungen, mit einem Aufsatz über die Aufgaben der Neurobiologie, Munich, E. Reinhardt, 1907, p. 225.

3. Muratoff, V.: Secundäre Degenerationen nach Zerstörung der motorischen Sphäre des Gehirns, Arch. f. Anat. u. Physiol. (Physiol. Abt.), 1893, p. 18.

4. Dejerine, J.: Anatomie des centres nerveux, Paris, Rueff & Cie, 1895, vol. 1, p. 758.

that the fiber band which they observed in the abnormal cerebrum is an association system connecting the opposite poles. He amplified their conception, moreover, by placing in that bundle connections between the temporal and frontal and the insular regions as well.

Sachs,[5] in his "Anatomie des Grosshirns," did not appear to pay any attention to the findings of Onufrowicz and Forel. Instead he spoke of "the most important fiber bundle which connects the corpus striatum with the cerebral cortex . . . the fasciculus nuclei caudati." His description of this bundle coincides entirely with the fasciculus subcallosus of Muratoff and the occipitofrontal fasciculus of Onufrowicz and Forel.

Bechterew[6] agreed entirely with Sachs regarding the fasciculus nuclei caudati, but added that the fasciculus is continuous behind with the tapetum, "as anyone may assure himself in the case of the absence of the corpus callosum." The quoted sentence must be taken in a figurative sense, for large defects of the corpus callosum are rare, and absence of that commissure is extremely so.

As far as I can gather, the investigations of Probst[7] appear in large part to corroborate Wernicke's[8] opinion that the subcallosal fasciculus contains fibers of the corpus callosum which radiate in the frontal lobe. On account of this fact he named the subcallosal fasciculus the longitudinal callosal bundle. He denied emphatically the function of the subcallosal fasciculus as an association system between the occipital and frontal poles of the hemisphere. He stated plainly[7a] that "the assumption of Forel and Onufrowicz that the longitudinal callosal bundle is, in the normal brain, a fronto-occipital bundle must be considered erroneous." And again,[7b] "I have carefully investigated a cerebrum in which the corpus callosum was absent and found that the longitudinal callosal bundle consists of callosal fibers and forms the tapetum."

Anton and Zingerle[9] described a bundle in the exact situation of the subcallosal fasciculus, which they named the "fasciculus longitudinalis medialis." According to these authors this bundle is identical

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5. Sachs, H.: Anatomie des Grosshirns, Breslau, Preuss & Jünger, 1893, p. 78.

6. Bechterew, W.: Les voies de conduction du cerveau et de la möelle, Lyon, A. Storck & Cie, 1900, p. 604.

7. Probst, M.: (*a*) Ueber den Bau des vollständig balkenlosen Grosshirns, Arch. f. Psychiat. **34**:709, 1901; (*b*) Ueber die Leitungsbahnen des Grosshirns, Jahrb. f. Psychiat. u. Neurol. **25**:18, 1903.

8. Wernicke, C.: Lehrbuch der Gehirnkrankheiten, Berlin, T. Fischer, 1881, vol. 1, p. 37.

9. Anton and Zingerle: Bau, Leistung und Erkrankung des menschlichen Stirnhirnes, Graz, Leuschner & Lubensky, 1902, p. 160.

with the occipitofrontal fasciculus and forms a connection between the posterior portion of the temporal lobe and the frontal regions of the cerebrum.

Mayendorf [10] denied the identity of the fasciculus medialis with the fasciculus occipitofrontalis, and he denied that either of these fasciculi is an association system.

The foregoing review furnishes a rather faint yet sufficient idea of the degree of uncertainty and confusion which prevails regarding the elements which make up the subcallosal or supracaudate band of nerve fibers.

PRESENT INVESTIGATION

In partial agreement with the authors who have maintained that the subcallosal fasciculus in question is connected with the caudate nucleus, it will be shown that the elements of that fiber band are to be found in the substance of the caudate nucleus. It will also be shown, however, that these elements pass through the entire thickness of the head and body of the caudate nucleus without any perceptible loss. The present investigation confirms the observation of the authors who found the fibers of the fasciculus in question radiating in the frontal and prefrontal regions of the cerebrum. It will be shown that the subcallosal bundle is not an association system, but that it contains parts of the thalamic, the corticospinal and the corticopontile fiber systems as they pass through the internal capsule to their respective destinations.

In justice to the authors who have taken pains to investigate the question, it must be admitted that the current method of cross-sectioning the cerebrum, which results in a microscopic picture composed of fine dots and very short streaks, makes the definition of any one fiber tract extremely difficult. The result of the radiation of a thin, compact and deep-seated bundle over a large area of the cerebral cortex is that a large cortical lesion may not, years or even months later, be detected by a tract of secondary degeneration in the thin bundle into which the extremely diffuse fibers are gathered in a given situation. If a bundle of an area of 10 sq. mm. in cross-section is distributed over one-half the surface of the cerebral cortex—about 30,000 sq. mm.—a cortical lesion covering an area of 100 sq. mm. will result in a tract of degeneration in that bundle only 0.03 sq. mm. in cross-section. In the course of months or years the contraction of that hairlike tract of degeneration must make its recognition under the microscope a matter of the greatest uncertainty.

Method.—The method employed in the present investigation obviates to a large extent the uncertainties of cross-sectioning the nerve fibers. The tract or the fiber

10. von Mayendorf, N.: Die Assoziationssysteme des menschlichen Vorderhirns, Arch. f. Anat. u. Physiol. (Physiol. Abt.), 1919, p. 302.

sheet is first dissected out along the lines of least resistance of the tissue, that is, along its grossly apparent course. It is then flattened between glass plates, fixed in that situation and sectioned along its flat plane. The microscopic sections are therefore largely along the course of the fibers. If small fiber bundles are cut across, the fact is immediately detected in a microscopic field which consists of a large preponderance of long lines.[11]

In the investigation of the subcallosal fasciculus the following procedure was employed:

The convolution of the cingulum was removed and the sagittal radiation of the corpus callosum lateral to the cingulum was exposed. The superior bundles of the callosal band—those which line the mesial wall of the hemisphere lateral to the cingulum—were removed. This procedure disposes of about one-half the thickness of the callosal band. The rest of the band contains the fibers which perforate the corona radiata and are interlaced with its fibers. They are, therefore, torn in an attempt to pull them away. The remaining thickness of the corpus callosum was

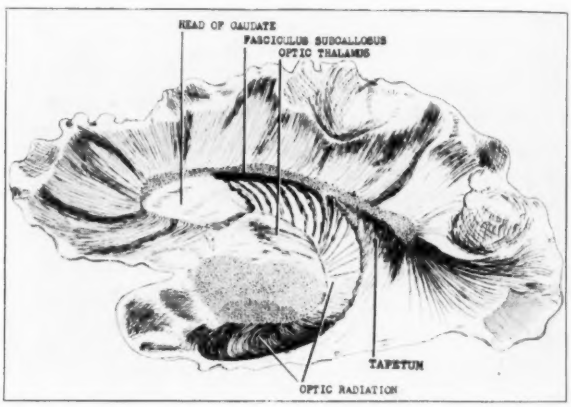

Fig. 1.—A drawing from a plaster of paris cast of a dissection. The body and tail of the caudate nucleus had been scraped away, exposing the stout superior bundles of the thalamic radiation which bend forward superiorly to make up the fasciculus subcallosus. The posterior and the inferior contingents of the thalamic radiation had been partly exposed by the removal of the corresponding portions of the tapetum.

then trimmed close to the ventricular wall. The ependyma covering the body of the lateral ventricle was peeled away. The soft tissue of the caudate nucleus was gently scraped, or rather pressed, away by means of a blunt tool, until a number of radiating, stout bundles appeared, extending between the upper lateral edge of the thalamus and the subcallosal fasciculus. In a carefully executed dissection these radiating bundles could be seen to bend abruptly forward at their upper extremity, almost at a right angle, beneath the corpus callosum, beyond which they were broken up into finer fasciculi which proceeded in the space between the corpus callosum and the upper and anterior edge of the caudate. These finer fasciculi,

11. Rosett, J.: A Study of Cerebral Fibre Systems by Means of a New Modification of Anatomical Methods, Brain **45**:357, 1922.

gathered above into a horizontal bundle, were seen in the gross specimen to make up the subcallosal bundle, as shown in figure 1, which is a drawing of a plaster of paris cast of a dissection.

The portion of the optic thalamus which projects into the ventricle was then cut off; the remaining, attached, lateral portion of the thalamus was next dissected away along the plane of the substantia nigra, together with the stout radial bundles already mentioned and the subcallosal band with which these bundles are merged. The dissection being continued along a sagittal plane in the line of least resistance, a sheet of fibers was dissected away from the mesial wall of the hemisphere. The entire preparation was then flattened between plates of glass and put into mordanting solution in preparation for microscopic sectioning and staining by the Weigert-Pal method.

After the removal, as far as is possible in a gross dissection, of the sagittal constituents of the thalamic radiation, the lower central portion of the mesial surface of the hemisphere still presented the appearance of stout, radiating bundles

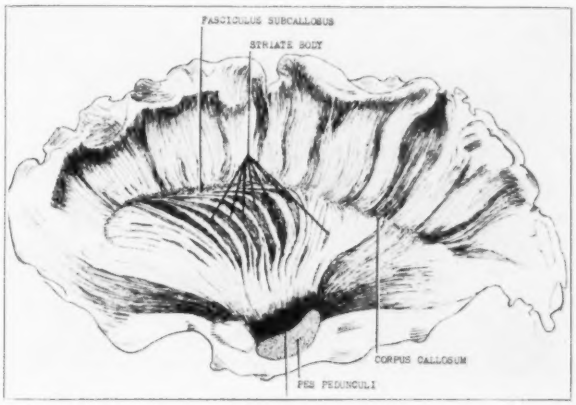

Fig. 2.—A drawing from a plaster of paris cast of a dissection of the peduncular (palliopontile and pyramidal) radiation. The superior contingents of the stout bundles are observed to bend forward above the striate body, where they contribute to the formation of the subcallosal fasciculus.

embedded in the substance of the striate body. At the upper and anterior levels of the striate body these bundles bent abruptly, almost at a right angle, and proceeded forward in the same manner as did the thalamic bundles. This appearance may be seen in figure 2, which is a drawing of a plaster of paris cast of the dissection. The corpus callosum, however, was no longer above the horizontal fasciculus. That commissure at this level was widely dispersed into its constituent fibers, radiating toward the lateral surface of the hemisphere.

The stout radial bundles embedded in the substance of the striate body converged below into the pes pedunculi of the midbrain. They therefore consisted of pyramidal and corticopontile fibers. The pes pedunculi was then lifted away from the soft substance of the globus pallidus and the putamen on which it rests laterally. The dissection was continued, a sheet being removed which included the radial bundles, their superior continuation into the horizontal anterior fasciculus (no longer subcallosal) and the fine fiber bundles into which the fasciculus radiates

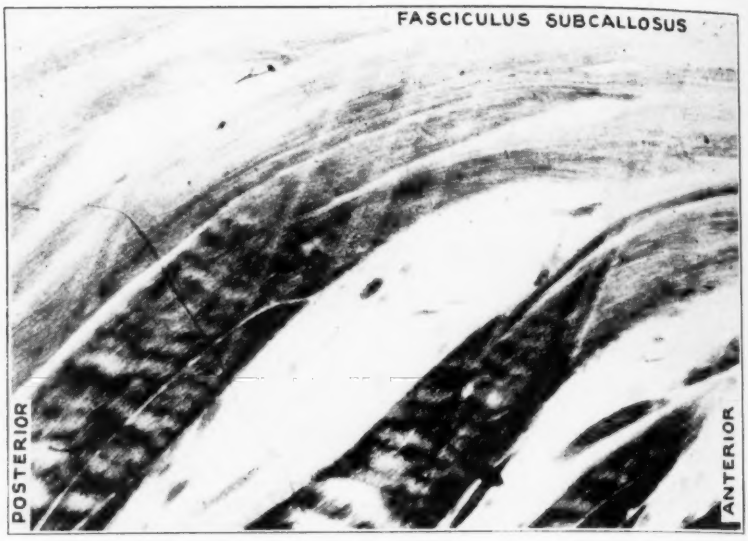

Fig. 3.—A photomicrograph of the superior contingent of the thalamic radiation, in the space between the optic thalamus and the corpus callosum (from sagittal sections of a flattened dissection [11]). The stout bundles on reaching the superior border of the caudate nucleus bend forward to form the fasciculus subcallosus.

Fig. 4.—The same area as shown in figure 3, but more anteriorly, in the region of the head of the caudate nucleus. Superiorly is the fasciculus subcallosus, the source of which can be easily traced to the thalamic bundles which perforate the caudate nucleus. Above and in front, the radiation of the fasciculus into the frontal and prefrontal regions can be clearly seen.

Fig. 5.—A portion of the palliopontile and pyramidal projection systems in their passage through the striate body. The photomicrograph was prepared from the dissection shown in figure 2. Superiorly the stout bundles bend forward, contributing to the formation of the subcallosal fasciculus.

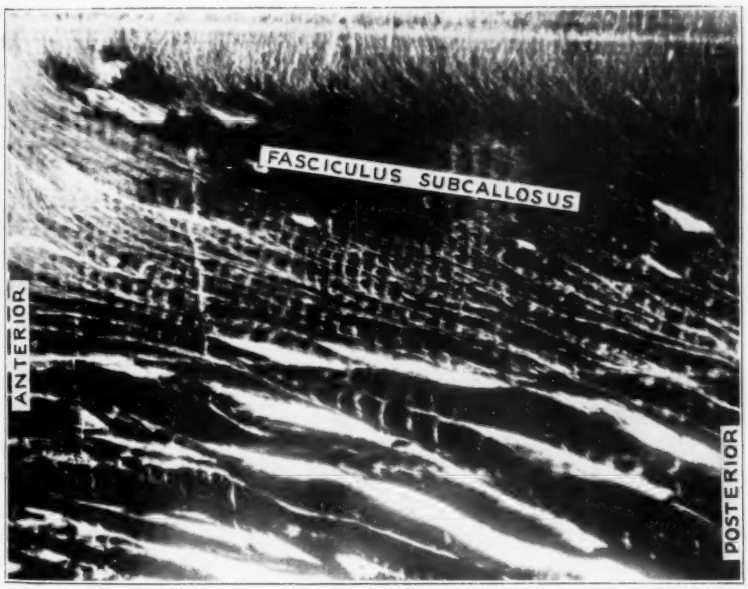

Fig. 6.—A higher magnification of the space included in the circle in figure 5. The composition of the fasciculus subcallosus is here clearly seen.

as far as the superior, anterior and posterior borders of the preparation. This sheet was then flattened between plates of glass and placed in the mordant.

Both the thalamic and the peduncular preparations were then sectioned on the microtome along their respective flat planes.

Results.—Figure 3 is a photomicrograph of the superior portion of the radial thalamic bundles as they pass from the lateral thalamic nucleus through the substance of the body of the caudate nucleus and bend forward, becoming the fasciculus subcallosus. Figure 4 shows the radial thalamic bundles which pass through the substance of the head of the caudate. The fasciculus subcallosus above and in front of the caudate is plainly seen in the photographs to be continuous with the radial thalamic bundles. Figures 5 and 6 are photomicrographs of

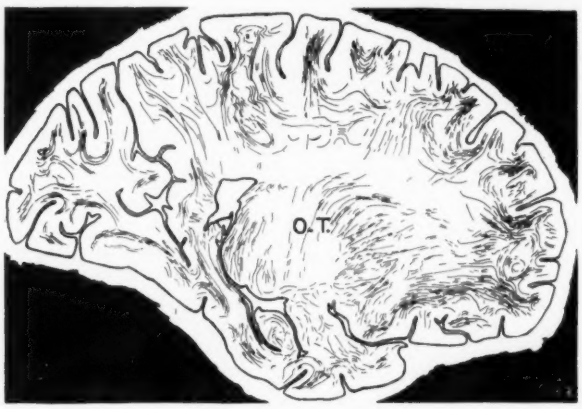

Fig. 7.—A sagittal section of an exploded cerebrum.[12] The lines of cleavage of the anterosuperior contingents of the thalamic radiation are indicative of the source of the subcallosal fasciculus. *O. T.* indicates the optic thalamus.

the peduncular radial bundles embedded in the substance of the striate body and bending superiorly and anteriorly forward in an almost horizontal direction. They constitute the deepest—most lateral—portion of the fasciculus subcallosus. Since, however, the callosal fibers are not aggregated into a compact band in this situation, but are dispersed and interlaced with all the constituents of the internal capsule, the horizontal bundle cannot properly be called subcallosal.

It will be observed in the photomicrographs that the horizontal fasciculi—the subcallosal bundle—of the thalamic and peduncular constituents separate above into fine fibers which form the radiation of the projection systems which they represent.

12. Rosett, J.: A New Anatomic Method for the Study of the Brain, Tr. Am. Neurol. A. **57**:425, 1931.

Another evidence regarding the nature of the horizontal subcallosal fasciculus is afforded by sagittal sections of an exploded cerebrum.[12] These sections show the lines of cleavage of the tissue. Figure 7 is a drawing of such a section. In it may be seen the lines of cleavage indicative of the situation of the radial thalamic bundles and their continuation in the horizontally placed subcallosal fasciculus.

CONCLUSION

On the basis of the foregoing data, the conclusion is justified that the subcallosal bundle is not an occipitofrontal association system, a radiation of the caudate nucleus or a contingent of the corpus callosum. Microscopic sections prepared from flattened dissections show the mesial and more superficial portion of this bundle to be made up of thalamic fibers. Its deeper and more lateral portion is made up of fibers which proceed from the prefrontal and frontal and perhaps the anterior portion of the parietal regions of the cerebral cortex to contribute to the formation of the pes pedunculi of the midbrain. They are, in other words, corticospinal and corticopontile fibers.

DISCUSSION

Dr. Israel Strauss, New York: One point that seems to be important is that, despite the fact that there is no single tract such as the fronto-occipital, clinicians for a long time have taken such a tract into consideration in explaining the clinical symptoms in their cases. Even though such a tract may not exist anatomically, there is no reason, it seems to me—and I dare say Dr. Rosett will agree to this—for one to give up the idea that those particular parts of the brain are connected in some way or other, not necessarily by one tract, but by numerous association tracts; thus the clinical phenomena which one explains on the assumption of a tract or tracts connecting these parts of the cerebrum may remain of benefit to one in clinical diagnosis.

Dr. Charles Davison, New York: Were the sections cut serially and stained by the myelin sheath method? Has there been any opportunity to observe lesions of the frontal lobe, arteriosclerotic or neoplastic, with myelin sheath degenerations in the occipital lobe? I have had the opportunity to observe lesions of the frontal lobe (softenings and neoplasms) with demyelinization of the fibers in the occipital lobe.

Dr. Joshua Rosett, New York: I think that Dr. Strauss is right. My studies of the association systems of the human cerebrum show that there are numerous short association systems extending between the frontal and the occipital lobe. From a clinical point of view, therefore, it is entirely justifiable to speak of connections between the opposite poles of the cerebrum. But the same studies have convinced me that there are no long, continuous tracts connecting the frontal with the occipital pole, and I do not think that any anatomist has so far shown such long association systems to exist.

In answer to Dr. Davison's questions: The lantern slides that I have shown were made from serial sections stained by the Weigert-Pal method. The sections were prepared from flattened dissections.

With respect to the method of massive degeneration by means of which some authors have attempted to ascertain the nature of the so-called fronto-occipital fasciculus, I wish to call attention to the following: Suppose there is a lesion—a tumor, a hemorrhage or an experimental injury—in the frontal area. Muratoff [8] has, as a matter of fact, made such observations. As a result of such a lesion one is bound to find degeneration in the fasciculus in question if it is true that the fasciculus consists of thalamic, corticopontile and corticospinal projection fibers on their way to their respective destinations. On the other hand, in lesions of the occipital lobe or of the posterior portion of the temporal lobe, one is almost certain to find degeneration in the corpus callosum. The tapetum of the corpus callosum extends above and in front as far as the posterior portion of the fasciculus subcallosus and is therefore likely to give the impression of continuity with that fasciculus.

DYSTROPHIA MYOTONICA

A CLINICOPATHOLOGIC STUDY

MOSES KESCHNER, M.D.
AND
CHARLES DAVISON, M.D.
NEW YORK

In 1926, Weil in collaboration with one of us (Keschner [1]) described a case of dystrophia myotonica characterized histopathologically by selective involvement of the vegetative nervous system. Since then only one other case with necropsy observations has been reported (Guillain, Bertrand and Rouquès, 1932 [2]). The object of this contribution is to record two additional cases of this disease occurring in a brother and sister, with the necropsy observations in one (brother).

REPORT OF CASES

CASE 1.—L. P., a man, single, aged 40, born in Russia, a newsdealer, was admitted to the Montefiore Hospital on July 26, 1923, complaining of weakness of the lower extremities and general fatigue. His father died at the age of 77 of "stomach trouble;" the mother died of some unknown cause at the same age. Two sisters died at the ages of 40 and 35 years, respectively; the cause of death could not be ascertained. A sister, aged 60, and a brother, aged 55, were well. Another brother, aged 35, living in Russia, had always complained of general weakness. A sister, aged 44 (case 2), was afflicted with the same disease as the patient. The patient's birth and development were uneventful. Except for an operation for intestinal obstruction in 1915, the previous history was of no significance.

In 1921, the patient experienced general fatigue and weakness of the lower extremities, which persisted for one year, when pulmonary tuberculosis developed, for which he was sent to the Sea View Hospital. Here he remained for eight months, during which the pulmonary condition became worse, and he was admitted to the Montefiore Hospital.

Physical Examination (1923).—The patient was poorly nourished, small and hypoplastic and weighed 92 pounds (41.7 Kg.); he showed evidences of extensive pulmonary tuberculosis and had unusually small testes (fig. 1).

From the Neuropathological Laboratory and Neurological Division, Montefiore Hospital.

Read by Title at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 11, 1933.

1. Weil, A., and Keschner, M.: Dystrophia Myotonica, Tr. Am. Neurol. A. 1926, p. 10; Ein Beitrag zur Klinik und Pathologie der Dystrophia myotonica, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:687, 1927.

2. Guillain, G.; Bertrand I., and Rouquès, L.: Les lésions de la myotonie atrophique, Ann. de méd. **31**:180, 1932.

Neurologic Examination (1923).—The right pupil was slightly larger than the left. There was bilateral ptosis. The wrinkles of the left side of the forehead were less prominent than those of the right. The jaw deviated to the left. The left half of the tongue was thinner than the right. The soft palate moved better on the left side. There was wasting of the facial muscles, giving rise to a typical

Fig. 1 (case 1).—Drooping of the head and stooping of the body, hatchet face, prominence of the thyroid and trachea and marked atrophy of the entire musculature.

"hatchet-like face." The sternocleidomastoids, extensors of the hands, quadriceps and tibial group of muscles were markedly atrophied. Voluntary motor power was diminished in all segments supplied by the atrophied muscles. The tendon reflexes of the upper extremities were normal. The knee jerks could be elicited only on reenforcement. The ankle jerks were present. The abdominal reflexes were active.

There were no pathologic reflexes. Sensation was unimpaired. The mechanical irritability of the affected muscles was increased, and there was a typical myotonic reaction of the thenar and hypothenar eminences on both sides.

Course.—There was a gradual progression of the disease. Examination six years later revealed inability to hold up the head owing to almost total absence of the sternocleidomastoid and trapezius muscles (fig. 1). The eyes could not be shut tightly. There were weakness of the muscles of mastication and difficulty in swallowing. Because of the atrophy of the muscles of the neck, the thyroid and larynx appeared unusually prominent (fig. 1). The marked atrophy of the appendicular musculature gave rise to an apparent reduction in motor power, although there were no evidences of motor or sensory paralysis. When the patient was ordered to open either hand after making a fist, there was noted great difficulty in initiating the movements necessary to perform this act; at first there was a gradual extension of the little finger, followed by a slow extension of the index finger, then of the middle finger, and then of the ring finger; finally the thumb was slowly abducted, until the entire hand was opened. With each successive repetition of the movement its execution became more facile. When the biceps humeri, deltoids, tongue, muscles of the thenar and hypothenar eminences and the calf muscles were struck with the percussion hammer, a wormlike or wavelike contraction of considerable duration was noted over the area tapped (myotonus). Myotonus was also observed on initiating movements in the distal parts of the lower extremities. There were no cerebellar signs. The hair was sparse and thin. No cataract was present. The testes were atrophied. There were no mental symptoms.

Laboratory Data.—Roentgen examination of the skull gave negative results. Electrocardiographic examination (Sept. 26, 1924) disclosed a low voltage in all three leads, marked respiratory deflections, no delayed conduction time and numerous tremors of the heart muscle.

The Wassermann reaction of the blood was negative. Examination of the blood revealed: hemoglobin, 58 per cent; red cells, 2,824,000; white cells, 7,400; polymorphonuclear leukocytes, 72 per cent; small lymphocytes, 14 per cent; large lymphocytes, 7 per cent; mononuclears, 5 per cent, and eosinophils, 2 per cent. The reaction to the sedimentation test of the blood was 9 per cent in the first hour and 21 per cent in the second hour. The blood sugar was 108 mg.; the urea nitrogen, 13.3 mg.; the uric acid, 4.6 mg.; the blood creatinine, 1.1 mg., and the serum calcium, 10.3 mg. per hundred cubic centimeters.

The first test of the basal metabolism showed: respiratory quotient, 0.83, and basal metabolic rate, —6 per cent; the second test, 0.835 and —6 per cent, respectively.

Lumbar puncture yielded a fluid under moderately increased pressure containing a faint trace of globulin and no cells. The Wassermann reaction was negative.

The blood pressure ranged between 110 systolic and 70 diastolic and 80 systolic and 54 diastolic, the average being 90 systolic and 60 diastolic.

Clinical Diagnosis.—The diagnosis was: dystrophia myotonica; chronic pulmonary tuberculosis.

Necropsy.—Gross Examination: The body was that of a poorly developed, cachectic man. The hair was sparse over the entire body and assumed a feminine distribution over the pubes. There were marked diminution of the subcutaneous tissue and wasting of the superficial muscles, most noticeable on the face, neck and hands, especially wasting of the interossei and the muscles of the thenar and

hypothenar eminences. There was winging of the scapulae, with slight scoliosis of the upper dorsal vertebrae, depression of the sternum and flaring of the lower ribs. The testes were soft and about the size of a lima bean. The lungs were partly collapsed and showed evidences of advanced tuberculosis. There were a marked increase in the epicardial fat and fatty infiltration of the wall of the right and left ventricles and of the papillary muscles. Actual fatty replacement of muscles of the left ventricle was also observed. The tongue was unusually thin.

Microscopic Examination of the Affected Endocrine Glands and Muscles: In the anterior lobe of the pituitary gland there was an increase in connective tissue

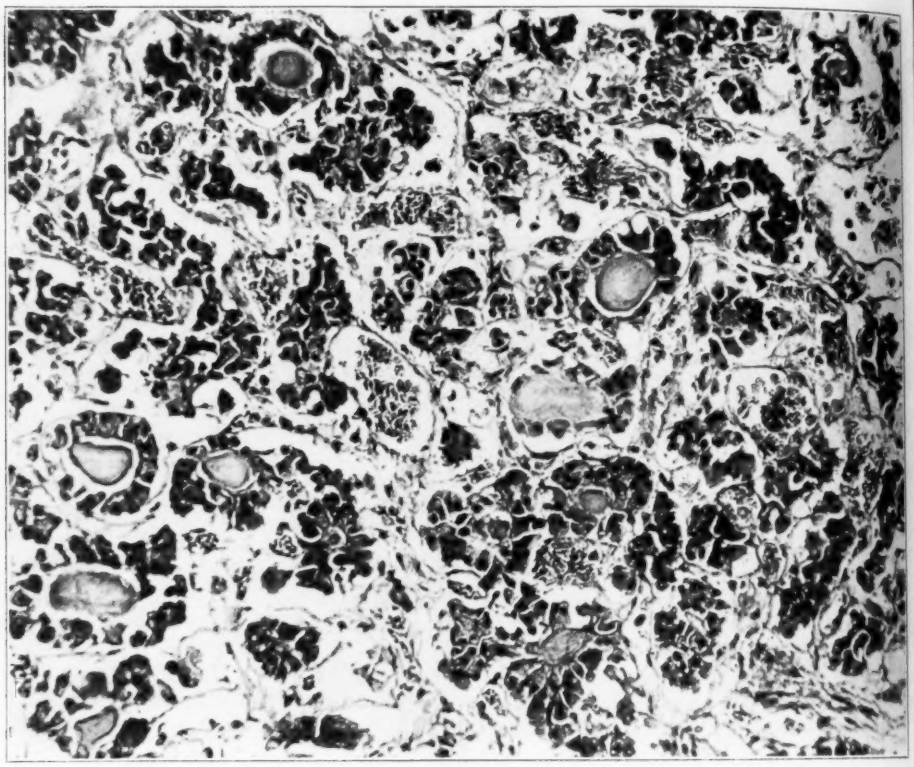

Fig. 2 (case 1).—Section from the anterior pituitary lobe, showing an increase in connective tissue, a diminution in the number of epithelial cells, degeneration of the eosinophilic cells and diffuse distribution of colloid substance in the acini. Spark stain; × 160.

with a diminution in the number of the epithelial cells (fig. 2). The basophilic cells appeared unusually large, with the nuclei at the periphery; the cells were distended with homogeneous basophilic substance. In the middle of the lobe the alveoli consisted almost entirely of eosinophilic cells in various stages of degeneration. In the anterior portion of the anterior lobe there was a considerable area of acellular connective tissue. There was diffuse distribution of colloid in the acini, most marked in the posterior and lateral parts of the anterior lobe and pars intermedia. The posterior lobe was fairly cellular.

The alveoli of the thyroid gland were distended with colloid, and the alveolar epithelium was flattened. The interstitial tissue was hyalinized and contained isolated accumulations of lymphocytes.

There was central fibrosis of the parathyroid glands, with strands of fibrous tissue radiating to the periphery. Several large and small follicles contained colloid and numerous large fat vacuoles.

Parts of the fascicular and reticular layers of the cortex of the suprarenal glands were replaced by a peculiar reddish, avascular and somewhat edematous

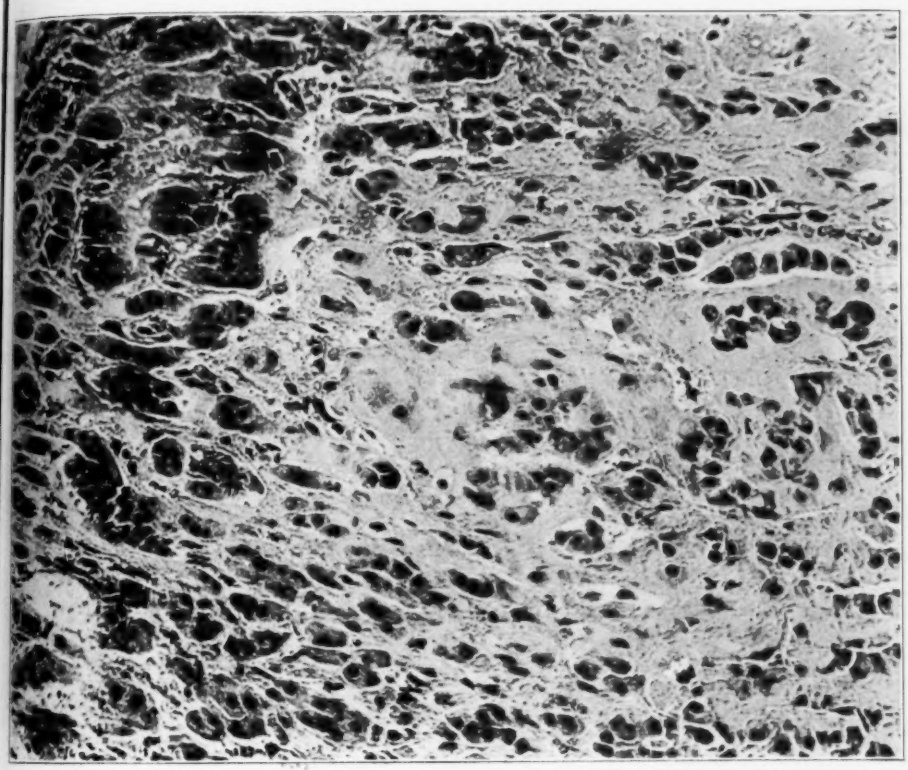

Fig. 3 (case 1).—Section from the suprarenal gland, showing fibrosis in the fascicular layer and falling out of fascicular cells. The cells are in various stages of degeneration. Hematoxylin-eosin stain; × 160.

substance. The unaffected portions of the cortex contained lipoid substance. There was fibrosis, chiefly in the fascicular layer, with falling out of fascicular cells which were in various stages of degeneration (fig. 3). The glomeruli near the capsule also showed degeneration.

The tunica vasculosa and albuginea of the testes were fused and thickened. There was complete aspermatogenesis. The seminiferous tubules were atrophied and replaced by interstitial connective tissue. There was an increase in the cells of Leydig (fig. 4). In the right testis, where the process was more extensive, there was also hyalinization of the fibrous tissue.

Sections from the temporal, sternocleidomastoid, trapezii, arm, forearm, hand, back, thigh, leg, tongue, diaphragm, heart and gastro-intestinal muscles were stained according to the hematoxylin-eosin, van Gieson, sudan IV and Bielschowsky methods. Most of the striated muscles of the body showed destruction of individual muscle fibers with fatty replacement (fig. 5). In many of the muscle fibers the longitudinal and transverse striations were completely lost (fig. 5). Some of the individual fibers were swollen, with waxy degeneration (fig. 6). The nuclei in the sarcolemma were increased; some of them were arranged in rows of from 10 to 20 (fig. 5); others had a tendency to form clumps and took a deep stain with

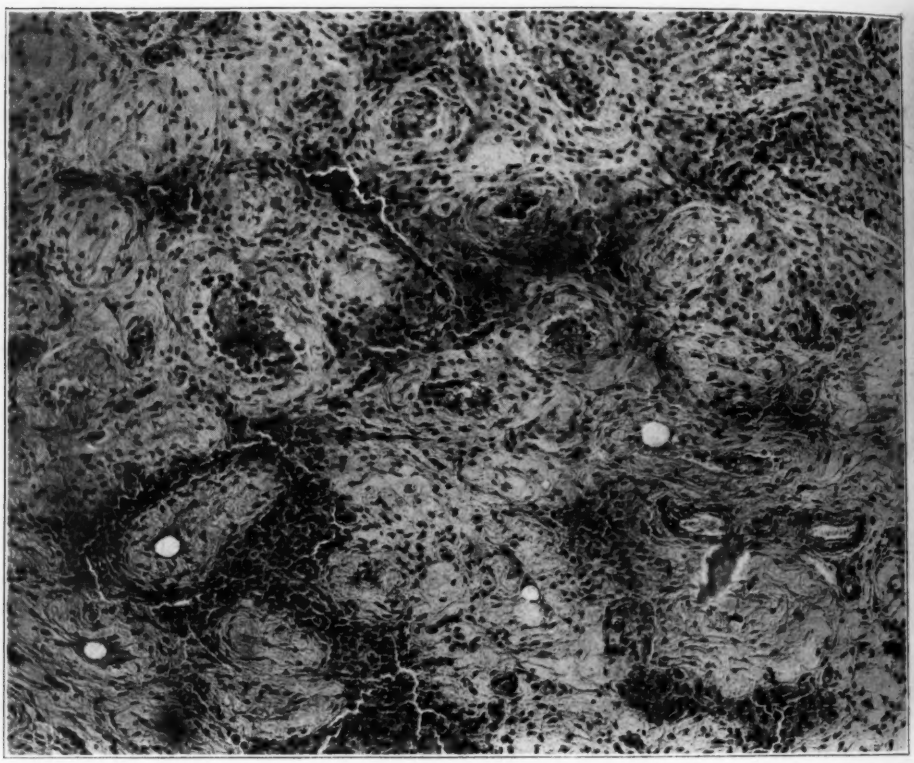

Fig. 4 (case 1).—Section from the testes, showing atrophy of the seminiferous tubules, replacement by interstitial tissue and an increase in the cells of Leydig. Hematoxylin-eosin stain; × 70.

hematoxylin (fig. 6). The clumps of sarcolemma nuclei were most evident where single muscle fibers had undergone complete destruction. There were few normal muscle fibers. Most of the muscle fibers in the sternocleidomastoids were replaced by connective tissue; the sarcolemma nuclei were more elongated and had a lesser tendency to form chains. The muscles of the arm and gluteal region disclosed marked hyalinization, with a tendency toward undulation of the longitudinal fibers. The muscles of the thenar eminence showed less fatty displacement, but a marked loss in striations. The thigh and peroneal muscles were destroyed; some of the

fibers contained foam cells, and others showed undulations. The myocardium was better preserved than the striated musculature. The muscle fibers of the right ventricle were replaced by fat (fig. 7). The smooth visceral muscles were partly destroyed and replaced by fat.

Central Nervous System: Gross examination. The brain and spinal cord showed no gross abnormalities.

Microscopic examination. Coronal sections through the striatum, diencephalon, hypothalamic nuclei, mesencephalon, cerebellum and medulla oblongata and sections from the various convolutions and spinal cord were stained according to the myelin

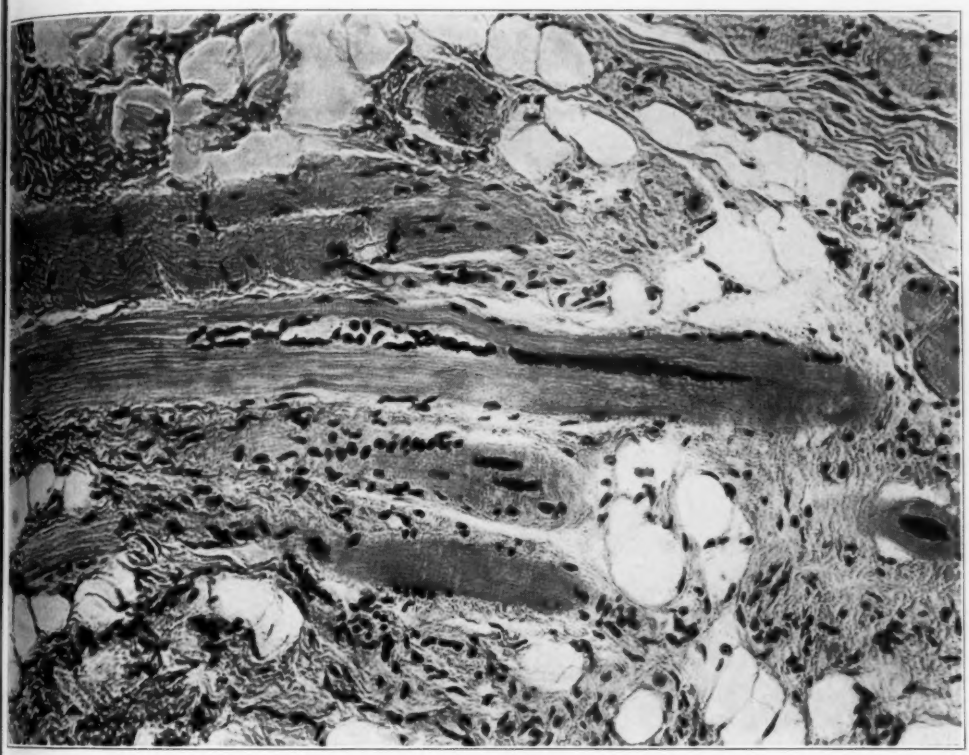

Fig. 5 (case 1).—Destruction of single muscle fibers with fatty replacement; increase in the sarcolemma nuclei and loss in striations. Hematoxylin-eosin stain; × 160.

sheath (Weil modification), cresyl violet, toluidine blue, sudan IV, Bielschowsky and Holzer methods. Blocks from the region of the tuber cinereum were cut serially.

The sections from the cerebral cortex were normal.

Sections through the anterior third of the neostriatum disclosed a tumor, the size of a pea, which originated from the corpus callosum and projected into the anterior horn of the right lateral ventricle (fig. 8). The tumor was a spongioblastoma. The parenchyma of the paleostriatum and neostriatum, as well as of the other structures at this level, was normal.

Section through the anterior half of the third ventricle showed that many of the ganglion cells of the paraventricular nuclei were swollen, and some were disintegrated. The Nissl substance was scanty and collected at the periphery of the cells; the nuclei were swollen, pale and eccentric (fig. 9 *A*). Some of the ganglion cells of the nucleus supra-opticus were disintegrated; others showed accumulation of pigment at the periphery, with eccentric nuclei (fig. 9 *B*). The nerve cells of the nuclei tuberis were well preserved.

Sections through the third ventricle, red nucleus and substantia nigra showed that the ganglion cells of the thalamic nuclei were somewhat swollen, contained

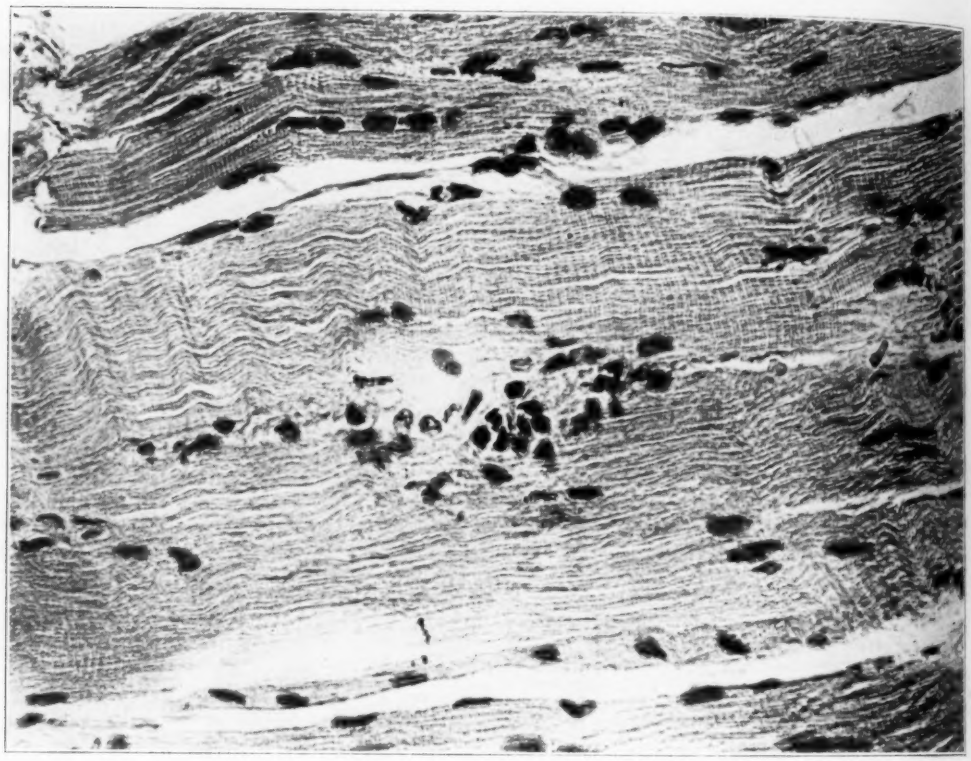

Fig. 6 (case 1).—Swollen single muscle fibers, loss in striations, waxy degeneration and clumps of sarcolemma nuclei. Hematoxylin-eosin stain; × 320.

pigment and had eccentric nuclei. The ganglion cells of the red nucleus and substantia nigra were normal. The nerve cells of the hypothalamic nuclei showed changes similar to those described in the previous sections; those of the ventral nucleus of the tuber took the Nissl stain poorly. The ganglion cells of the nucleus oculomotorius medius showed slight swelling, loss of Nissl substance, pigment atrophy and displacement of the nuclei toward the periphery.

In sections of the pons through the fourth ventricle at the origin of the fifth nerve and brachium conjunctivum, the ganglion cells of the locus caeruleus contained coarse pigment granules with a tendency to coalesce. In some of the nerve cells the pigment was a compact mass; the nuclei were generally displaced to the

periphery, and contained a pale-staining nucleoplasm. Many of the cells were also slightly shrunken.

Except for a number of somewhat swollen Purkinje cells, the cerebellum appeared normal. There was a lacunar state of the white matter of the dentate nuclei, with calcification of the vessels. The ganglion cells of the hypoglossal and dorsal vagal nuclei were normal, and those of the nucleus tractus solitarius stained poorly. A number of cells of the nuclei cuneatus and gracilis were pyknotic. Some of the ganglion cells of the nuclei fasciculi graciles and substantia gelatinosa rolandi were swollen, with absence of Nissl substance, eccentrically situated nuclei and deeply stained nucleoli; other ganglion cells showed a collection of Nissl sub-

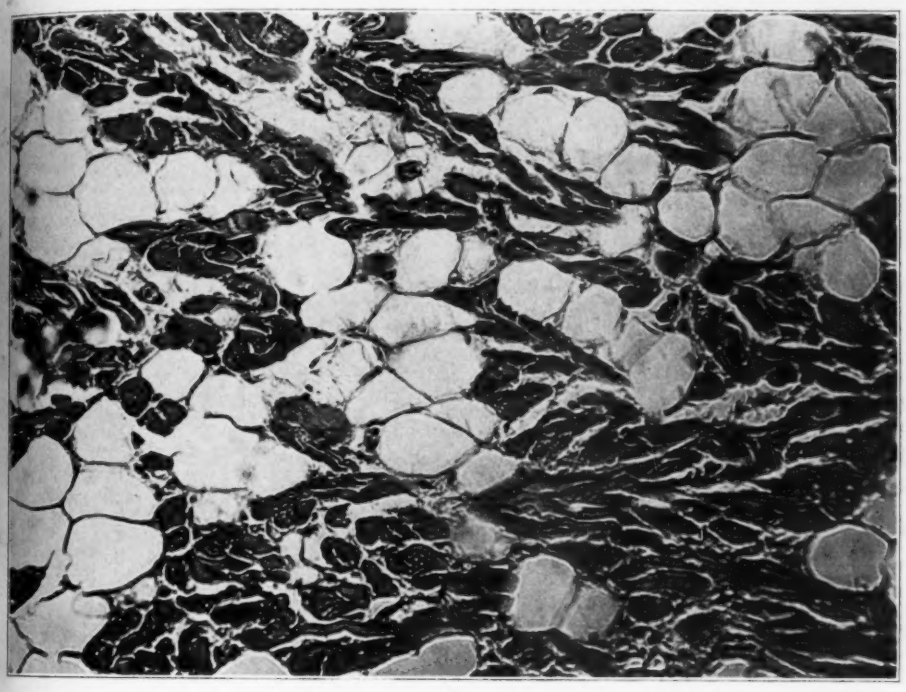

Fig. 7 (case 1).—Fatty displacement of muscle fibers of the heart. Hematoxylin-eosin stain; × 160.

stance at the periphery. The processes in most of these cells had disappeared, and the cells showed retrograde degeneration. Slightly vacuolated foamy cells were also found. The glia cells were moderately increased, with a predominance of astrocytes and microglia. The ventral ganglion cells of the spinal accessory nucleus, except for some which were slightly pyknotic, were well preserved.

Sections from the first cervical segment of the spinal cord disclosed hyperpigmented ganglion cells in the nucleus of Stilling. Some of the anterior horn cells were pyknotic. At the fourth cervical segment the ganglion cells of the dorsomesial, ventromesial and ventrolateral cell columns were slightly pyknotic and shrunken. Occasional disintegration of a ganglion cell was also observed. At the seventh cervical segment there was hyperpigmentation of the Nissl substance in

all ganglion cells, with pigment atrophy of some, especially in the ventrolateral and intermediate dorsolateral cell columns. An occasional shrunken anterior horn cell was also observed. At the second and fourth thoracic segments the vessels were markedly congested, with diapedesis and small hemorrhages within the gray matter, especially in the lateral cell columns. Some of the right lateral cell columns (splanchnic) in these segments were swollen; in many the Nissl substance was completely gone, or it had collected in clumps at the periphery (fig. 10*A*); most of the nerve cells in the left lateral column were destroyed, those remaining

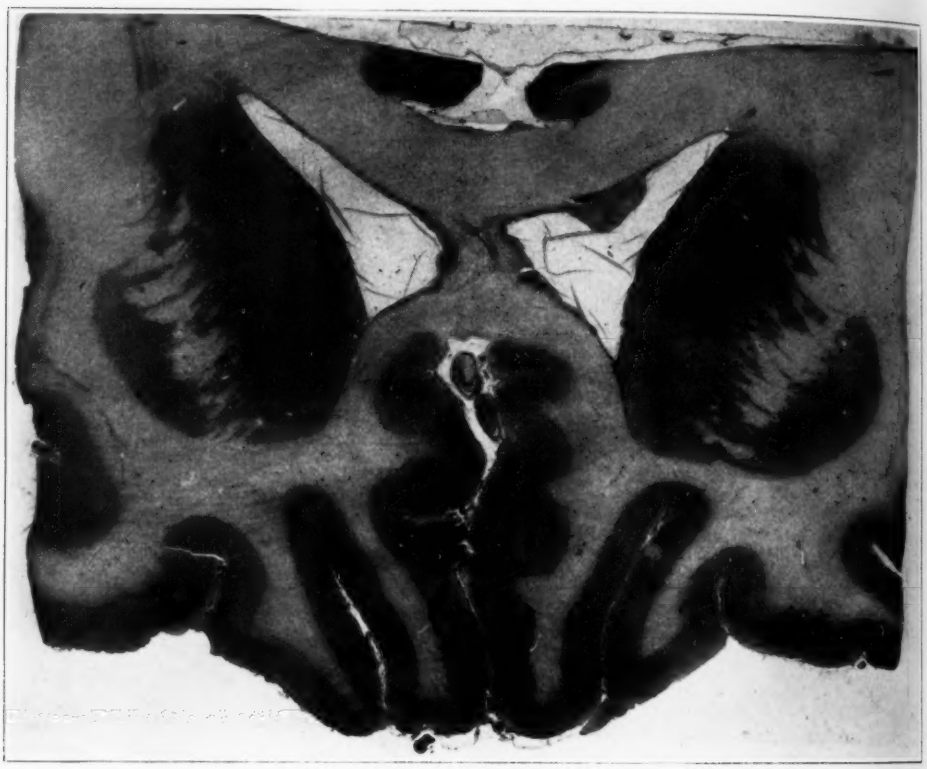

Fig. 8 (case 1).—Section through the anterior horns of the lateral ventricles, showing a tumor originating from the right corpus callosum and projecting into the ventricle. Cresyl violet stain; × 3.

being shrunken and pyknotic, with corkscrew processes (fig. 10*B*). At the fourth thoracic segment there was slight falling out of ganglion cells in the ventrolateral, ventromesial and dorsomesial cell columns; the remaining cells were shrunken and distorted, and had corkscrew processes and disintegration of the Nissl substance, with a tendency of the latter to collect at the periphery of the cells as well as in the processes. The nuclei in some of the nerve cells showed a homogeneous coagulated cytoplasm, with deeply stained nucleoli; in others the nuclei were at the periphery. The cells in Clarke's column were normal. An occasional nerve cell of the substantia gelatinosa rolandi was characterized by a homogeneous coagulated

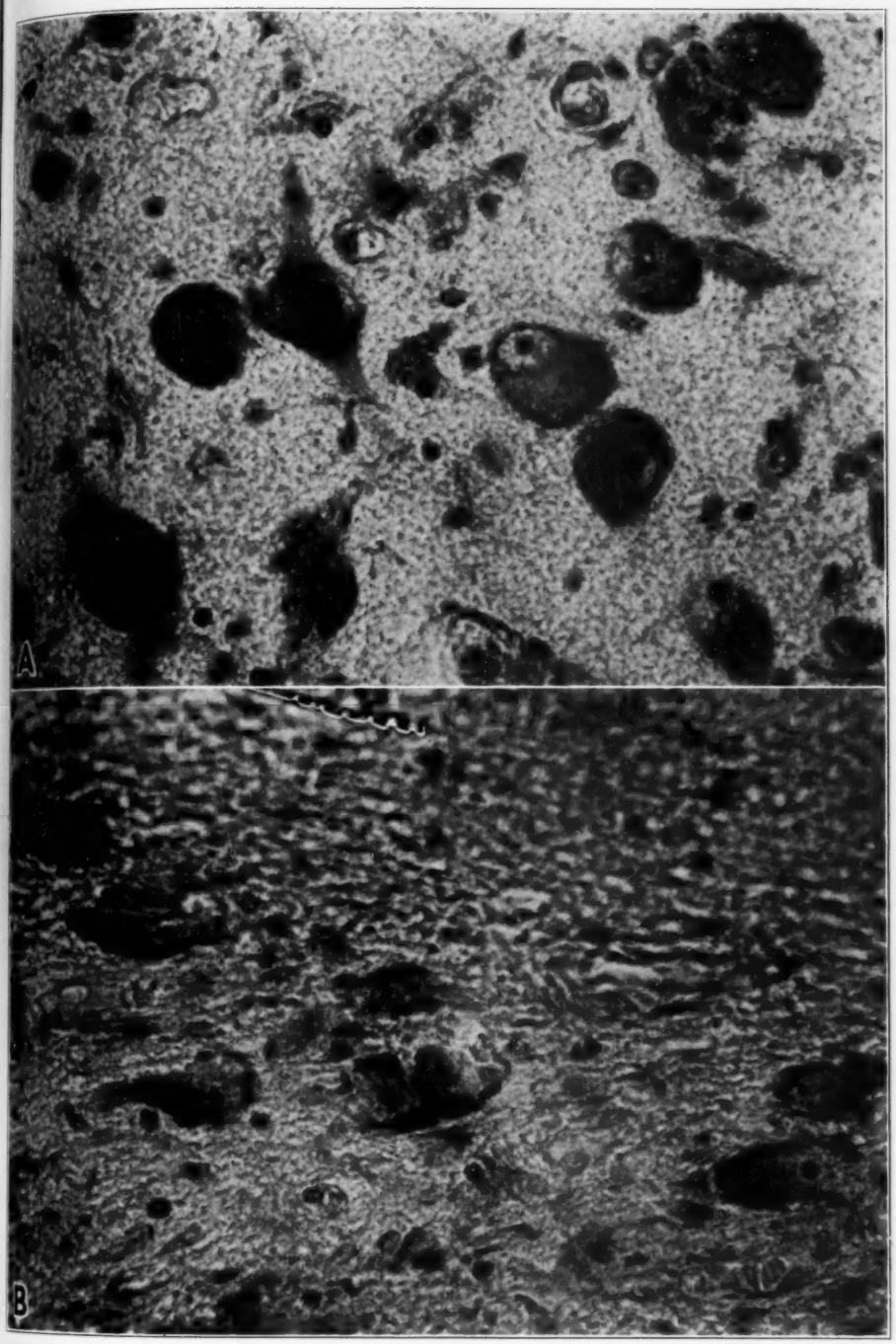

Fig. 9 (case 1).—*A*, nerve cells of the paraventricular nuclei. There are disintegration, swelling, scantiness of Nissl substance in some and eccentric nuclei. Cresyl violet stain; × 480. *B*, nerve cells of the nucleus supra-opticus, showing disintegration, accumulation of the pigment at the periphery and eccentric nuclei. Cresyl violet stain; × 480.

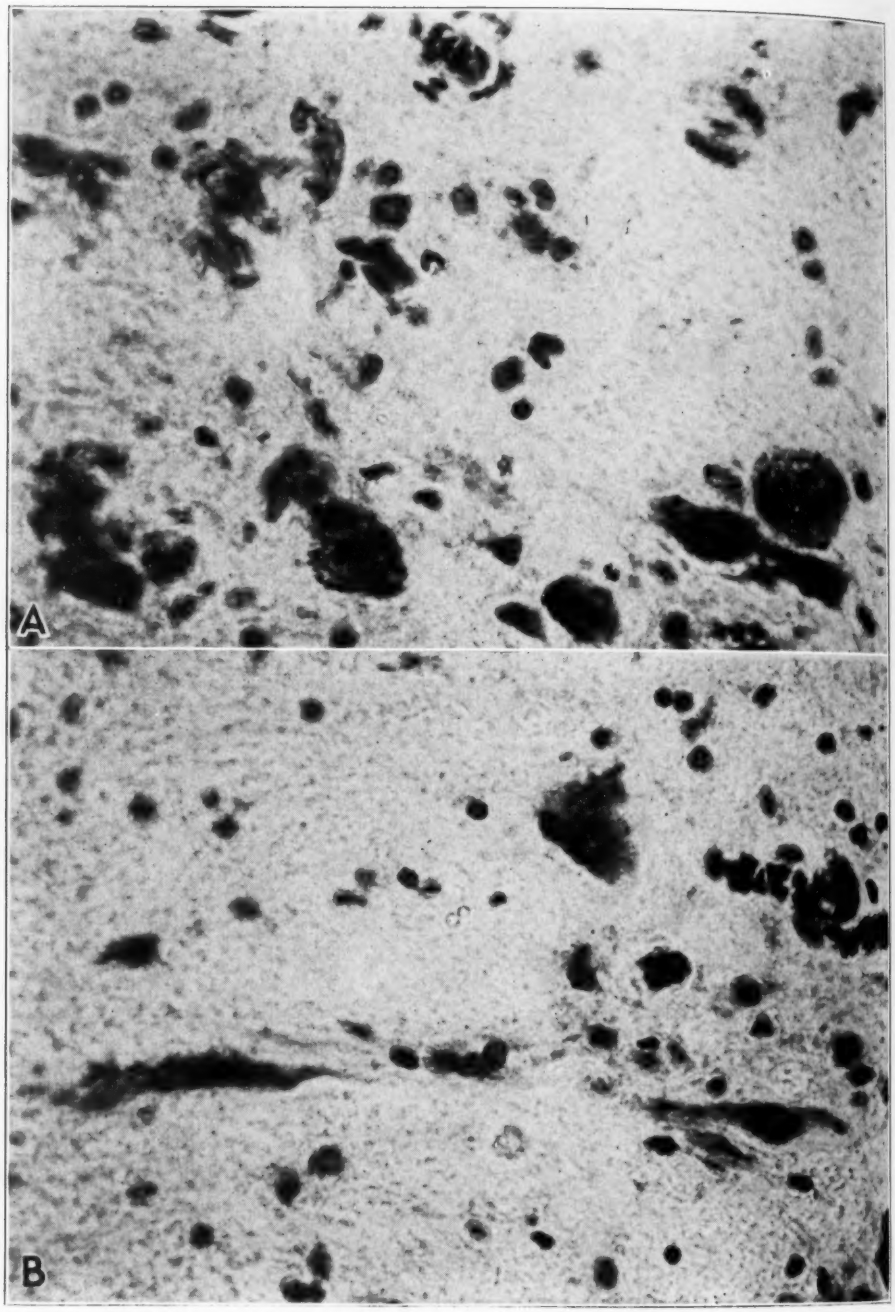

Fig. 10 (case 1).—*A* disintegration and swelling of the ganglion cells of the right lateral cell column (splanchnic) at the second dorsal segment. Cresyl violet stain; × 840. *B*, sclerotic and disintegrated nerve cells of the left lateral cell column (splanchnic) at the second dorsal segment. Cresyl violet stain; × 480.

cytoplasm. There was a slight increase of glia cells throughout the gray matter. Similar changes were observed in the lateral cell column (splanchnic) between the fifth and seventh thoracic segments, except that the hemorrhages were not as extensive. The anterior horn cells from the fifth to the twelfth dorsal segments were normal. The ganglion cells of the right lateral cell column between the ninth and eleventh thoracic segments showed similar though less extensive changes, those on the left side presenting sclerotic changes with long corkscrew processes. Except for pigment atrophy the anterior horn cells at the fourth lumbar segment were normal.

Summary.—The case is typical of dystrophia myotonica in a man in whom the disease began at the age of 38 and lasted eleven years.

Histopathologically, the outstanding changes in the endocrine glands were: an increase in connective tissue; a diminution in number and degeneration of the epithelial cells of the anterior lobe and pars intermedia of the pituitary (fig. 2); fibrosis of the fascicular layer and falling out of the fascicular cells in the cortex of the suprarenal gland (fig. 3); complete aspermatogenesis, with atrophy of the seminiferous tubules and replacement by fibrous connective tissue as well as an extensive accumulation of Leydig's cells in the testes (fig. 4).

The somatic musculature disclosed destruction of individual muscle fibers, fatty replacement, loss of the longitudinal and transverse striations, swelling and hyalinization of the remaining muscle fibers and increase in the sarcolemma nuclei, with a tendency to arrange themselves in rows or clumps (figs. 5 and 6). Similar, though less pronounced, changes were also observed in the splanchnic muscles. The striking changes in the nervous system consisted of: (*a*) marked alterations in the ganglion cells throughout the lateral cell columns (splanchnic) (fig. 10); (*b*) hemorrhages (agonal ?) in the gray matter of the spinal cord, especially in the midthoracic segments; (*c*) destruction of some of the anterior horn cells of the ventrolateral, ventromesial and dorsomesial cell columns at the fourth thoracic segment, and (*d*) changes in the nerve cells of the paraventricular and supra-optic nuclei (fig. 9).

Lesions were present also in the thalamus, locus caeruleus, nucleus tractus solitarius and nuclei of the fasciculi cuneatus and gracilis and substantia gelatinosa rolandi. These, however, were too slight to be of pathologic significance. A small spongioblastoma (fig. 8) presented no symptoms or signs during life. It is noteworthy that in the case of dystrophia myotonica previously reported by one of us (Keschner [1]) a spongioblastoma of the left temporal lobe presenting no symptoms during life was also found.

Case 2.—B. P., a woman, aged 44, single, born in Russia, a sister of the patient in case 1, was admitted to the Montefiore Hospital on Oct. 21, 1929. Birth and development were normal. Menstruation began at 14; it was regular, painless, moderate in amount and of two days' duration. Since 1929, the menses had been appearing only every other month.

Sixteen years prior to admission, the lower extremities gradually became weak; this progressed and at times was so marked that she would fall to the ground. Five years later weakness in the upper extremities and difficulty in swallowing and chewing developed.

Examination.—The patient was "chair-ridden," poorly nourished and underdeveloped, with a "hatchet-like facies" (fig. 11), slight drooping of both upper eyelids, a high, arched palate with crowded teeth, and an unusually thin tongue but no fibrillations. Gait was impossible on account of the profound weakness. In the sitting posture she was unable to hold up her head. The muscles of the face and neck, particularly the sternocleidomastoids, the shoulder muscles, the intrinsic muscles of the hands and the trunk, vastus and gastrocnemius groups were atrophied and hypotonic. The atrophied muscles felt doughy and were tender on

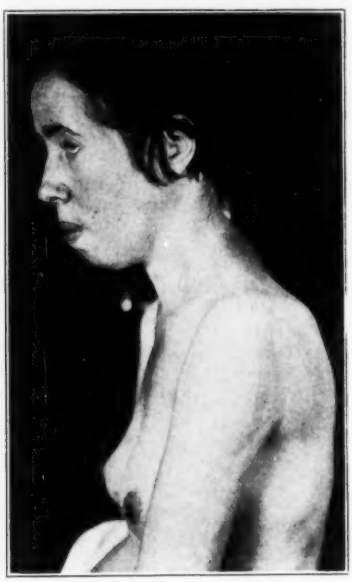

Fig. 11 (case 2).—Hatchet-like facies and atrophy of the muscles of the face, neck and shoulders.

deep pressure. Fibrillations were observed in the intrinsic muscles of both hands and in the pectoral group on the left side. Mechanical irritation elicited a mild myotonic reaction in the tongue. All deep reflexes were absent; only the left abdominal reflex was elicited. There were no pathologic reflexes, disturbances in coordination or objective sensory findings. There was no cataract. Electrical examination revealed no myotonic responses. The muscles responded to galvanism and faradism, but only to strong currents.

Laboratory Data.—Roentgenographic examination of the chest showed no abnormalities. Electrocardiographic tracings showed left ventricular preponderance with a high voltage. The blood pressure was 100 systolic and 65 diastolic. The spinal fluid was normal. Examination of the blood showed: hemoglobin, 80 per cent; red cells, 4,000,000; polymorphonuclear leukocytes, 70 per cent; lymphocytes, 30 per cent. The Wassermann reaction of the blood and the spinal fluid was negative. Analysis of the blood chemistry showed: urea nitrogen, 11.3 mg.;

uric acid, 2.3 mg.; creatinine, 1.2 mg., and calcium, 9.9 mg. per hundred cubic centimeters. The test of the basal metabolism showed: respiratory quotient, 0.79; basal metabolic rate, —24 per cent. Pharmacodynamic tests (epinephrine, pilocarpine and atropine) revealed no abnormalities.

Course.—Since admission there had been a gradual progression of the weakness, especially of the muscles supporting the head. With the advance of the disease a definite myotonic reaction in the biceps and muscles of the thenar and hypothenar eminences had also appeared. In 1932, the patient was given daily rations of 100 Gm. of gelatin and 30 per cent glycocol for a period of four months, but aside from some gain in weight there was no change in the condition.

Biopsy.—A piece of muscle taken from the midthigh, stained according to the hematoxylin-eosin and van Gieson methods, was found to consist mostly of connective tissue. The muscular elements were markedly distorted and replaced by fat. There were chains of sarcolemma nuclei. Undulations of the muscle fibers were preponderant. The longitudinal and transverse striations could barely be made out.

Diagnosis.—The diagnosis was myotonia atrophica.

Comment.—Case 2 is one of dystrophia myotonica. The late appearance of the myotonic reaction in most of the affected muscles and the marked tenderness to pressure over the wasted muscles without evidences of involvement of the sensory system are striking.

COMMENT

A brief review of the cases of dystrophia myotonica reported in the literature would seem to show that the disease is characterized by alterations in the muscles, endocrine glands and nervous system. Almost all observers agree on the constancy and uniformity of the changes in the muscles. Further discussion of this phase, therefore, is superfluous.

The endocrine glands showing the most outstanding histopathologic changes are the testes. In this connection it may be mentioned that Adie and Greenfield,[3] in reporting their cases, expressed skepticism about the rôle played by the endocrine glands. They stated, "this is unfortunate, as the assumption that the disease arises from a faulty activity of these glands rests up to the present on a purely clinical foundation."

The reports in the literature of the histopathologic findings in the nervous system are extremely conflicting. Although changes were found in the nervous system in all cases subjected to histopathologic investigation, the lesions apparently did not affect the same neural components in every case. It would seem that definite changes in the anterior horn cells were found only in the cases reported by Hitzenberger[4] and Guillain.[2] Lesions of the lateral cell columns were found only in the case reported by Weil and Keschner[1] and in case 1. The extensive lesions of the other vegetative nerve centers described by Weil and

3. Adie, J., and Greenfield, J. G.: Dystrophia Myotonica, Brain **46**:73, 1923.
4. Hitzenberger, K.: Ueber myotonische Dystrophie, Monatschr. f. Psychiat. u. Neurol. **47**:249, 1920.

Keschner were not found in this case, except for the alterations in the paraventricular and supra-optic nuclei. The latter, however, are so frequently observed in normal brains that we question their pathologic significance. The involvement of the nerve cells of the nucleus oculomotorius medius in Guillain's case as well as in ours is noteworthy.

A careful scrutiny of the changes in the anterior horn cells in the cases reported by Hitzenberger [4] and Guillain [2] would seem to point to a retrograde degeneration. Gagel,[5] Foerster [6] and others have shown that following transection of the anterior roots there was a decrease in the number of the lateral horn cells (splanchnic). Cutting of the posterior roots by Foerster [6] had no effect on the lateral horn cells. According to Foerster [6] and Gagel,[5] the alterations in the lateral horns are due to changes in the anterior roots and possibly also are secondary to degeneration of the muscles. As the anterior roots in our cases were intact, we are inclined to consider the retrograde degeneration of the lateral horn cells as secondary to destruction of the muscles. The hemorrages (agonal ?) in the gray matter in case 1 may perhaps have played a rôle in the destruction of the lateral horn cells, as they undoubtedly did in the anterior horn cells at the fourth thoracic segment.

A critical review of the clinical and pathologic reports would seem to point to the muscles as the site of the primary lesion of the disease. We favor this view because of the constancy with which pathologic changes are found in the muscles and the less constant variations in the distribution of the lesions of the central nervous system. The finding of changes in the sympathetic ganglion cells in only two cases (Weil and Keschner [1] and case 1) is an insufficient basis for accepting the views of Curschmann,[7] Bramwell [8] and others that the dystrophies in general may be due to disease of the sympathetic system.

It is difficult to evaluate the relationship between the changes in the endocrine glands and those in the muscles and central nervous system. Whether the same agent affects the endocrine system and the muscles, or whether the changes in the former are secondary to the general debilitating condition presented by these patients is a moot question. The loss of hair and the atrophy of the testes would seem to point to involvement of the pituitary or of the pathways from the tuber region to the pituitary. It is doubtful whether the insignificant changes thus far described in the pituitary and hypothalamic region are sufficient to account for the clinical manifestations of the disease.

5. Gagel, O.: Retrograde Degeneration an den Seitenhornzellen des Menschen nach Vorderwurzeldurchschneidung, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:565, 1931.

6. Foerster, cited by Gagel.[5]

7. Curschmann, H.: Beobachtungen und Untersuchungen bei atrophischer Myotonie, Deutsche Ztschr. f. Nervenh. **53**:114, 1914.

8. Bramwell, E.: Observations on Myopathy, Proc. Roy. Soc. Med. **16**:1, 1922.

The essential clinical features of dystrophia myotonica are the muscular wasting and the myotonia; in other words, the disease is a form of muscular dystrophy plus myotonia; it is the latter to which the disease owes its name. Many theories have been advanced to explain the mechanism of myotonia. The symptoms of myotonia have been reproduced in animals after poisoning them with veratrin and creatinine. In this connection it may be pointed out that in our cases the blood creatinine was normal. Some investigators believe the condition to be due to an exaggerated excitability of the sarcoplasm. If this were so, one would expect the myotonic reaction in every case of muscular dystrophy. Erb believes that the cause for the myotonus must be sought in the nerves themselves and not in the muscles, although he insists that microscopically the terminations of the nerves appear normal. It may also be pointed out that although myotonia is a cardinal manifestation of dystrophia myotonica, it is also a characteristic symptom in myotonia congenita (Thomsen's disease), which is characterized by an unusual hypertrophy of the muscles. The occurrence of this phenomenon in conditions other than dystrophia myotonica, such as in disease of the brain, cord and even the peripheral nerves, would seem to point to some other factor or factors, perhaps a functional disturbance in the muscles themselves, which may bear no relation to the structural changes in them. This functional disturbance may possibly be due to some changes in the body chemistry, the precise nature of which remains to be determined.

SUMMARY AND CONCLUSION

1. Two cases of dystrophia myotonica in siblings are described. One of the cases was subjected to a complete histopathologic study, and in the other a biopsy of one of the affected muscles was performed.

2. The outstanding pathologic findings were changes in: (*a*) the muscles, (*b*) the endocrine glands (pituitary, suprarenals and testes) and (*c*) the nervous system.

3. The lesions in the nervous system consisted of: (*a*) alterations in the ganglion cells of the lateral cell columns (splanchnic), and (*b*) changes in the nerve cells of the paraventricular and supra-optic nuclei. The neural lesions may possibly be regarded as retrograde degenerations.

4. From a critical review of the necropsy observations in the cases recorded in the literature and in our case 1 it would seem that the disease is one of a primary involvement of the muscles, a true muscular dystrophy (a myopathy).

5. The histologic observations in the cases reported as well as in our case 1 give no clue as to the cause of the myotonia, a clinical manifestation which distinguishes the disease from the other clinical varieties of muscular dystrophy.

CONTROLLED SPINAL ANESTHESIA

ITS VALUE IN ESTABLISHING APPROPRIATE LEVELS FOR CHORDOTOMY

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AND

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To relieve intractable pain, section of the anterolateral column of the spinal cord (Spiller-Frazier operation) has proved to be of practical clinical value. As all pain fibers enter the spinothalamic tract of the opposite side to terminate eventually in the thalamus, it is extremely important to determine at what point pain fibers from a certain area of the body finally join the anterolateral column on their way to the thalamus. It is recognized that these fibers travel not only in the peripheral nerves, but may follow divergent pathways along the arteries and find their way into the spinal cord at various levels. In order to determine the exact level at which all pain fibers have entered the spinothalamic tract from a given area, a clinical test has been devised.

A method of obtaining a gradually ascending anesthesia of the spinal roots under accurate and constant control is necessary in order to establish the time at which complete superficial and deep analgesia has been obtained. The method should afford the opportunity of carefully determining this fact, segment by segment, as each group of posterior spinal roots is temporarily anesthetized. The opportunity of testing the pain, heat and cold over the superficial areas of the body as well as observing the subjective reaction on the part of the patient to spontaneous pain is most desirable. The application of spinal anesthesia for this purpose requires an accurate and constant control of its action on the spinal roots, so that the operator may arrest or advance the process at any time.

Based on the principle that fluid tends to seek its own level, a test was devised which permits the constant control of spinal anesthesia to any spinal segment desired.

TECHNIC

The patient is placed on a table tilted at an angle of 30 degrees, with the head down. A spinal needle is introduced into the fourth or fifth lumbar interspace, and

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another spinal needle is introduced into the cisterna magna. The cisternal needle is connected by a rubber tube to a graduate buret containing 50 cc. of sterile physiologic solution of sodium chloride. When spinal fluid flows readily from both needles, connection with the buret is made to the cisternal needle and the buret is raised so that the level of saline solution is higher than the level of the lumbar needle (fig. 1). Spinal fluid flows out of the lumbar needle as the solution flows into the cisterna magna. The buret is then lowered so that the level of the saline solution is below the lumbar needle and fluid immediately returns into the buret, air being drawn into the lumbar needle as the column of the spinal fluid begins to

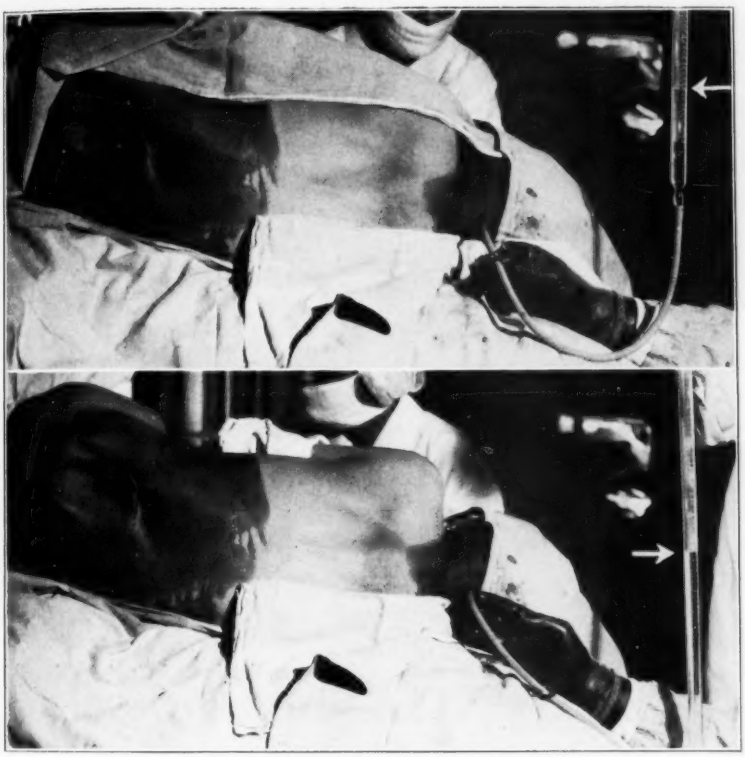

Fig. 1.—The upper illustration shows the buret elevated above the level of the lumbar needle; the system is tested to determine whether or not a free flow of spinal fluid occurs out of the lumbar needle. Note the level of fluid in the buret, and the pinch clamp for closing the system. The lower illustration shows the buret lowered to the desired level. The upper level of fluid in the buret is on a plane with the highest point of anesthesia required. The anesthetic is introduced through the lumbar needle as the column of fluid descends.

descend to seek the level of the saline solution in the buret (fig. 1). One cubic centimeter of spinal anesthesia (ascending type) is then introduced into the lumbar needle, and is drawn along the spinal canal to the spinal segment desired. This level is established by lowering the top of the column of saline solution in the buret to an imaginary plane passing through the spinal cord at the desired segment

(fig. 2). As anesthesia develops, subjective sensations of the patient are of importance as well as objective determinations. Testing with a pin-point and heat and cold readily determines when fixation has been produced as high as the segment desired.

Anesthesia may thus gradually be established as high as the fifth cervical segment. Above this point, paralysis of the motor supply to the diaphragm may impair respiration and so is undesirable. Thus, the anesthesia may be definitely checked and arrested at any level of the spinal cord below the fifth cervical segment, or may be carried higher if the operator so desires.

When the anesthesia has been established at the desired level and confirmatory sensory tests obtained, the buret may be raised to a point a few inches above the lumbar needle, so that fluid again fills the spinal canal and flows from the

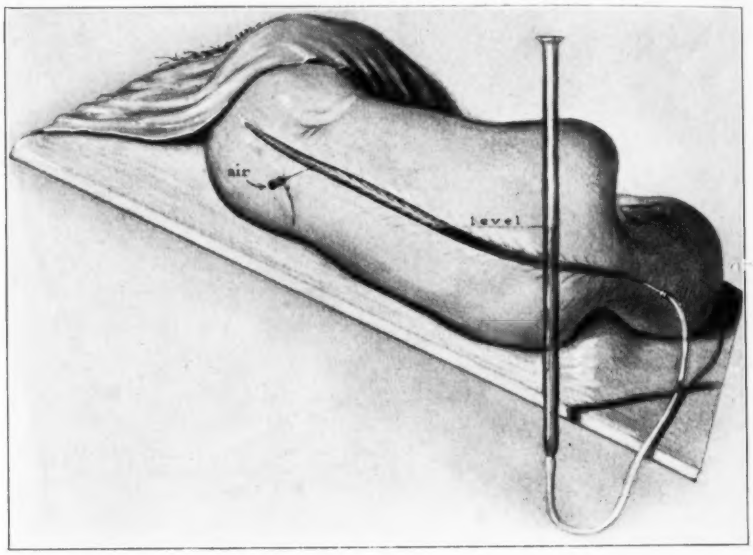

Fig. 2.—Diagrammatic representation of an equalization of fluid levels within the spinal canal and the buret.

lumbar sac. The sterile saline solution (mixed with spinal fluid which has been withdrawn) is reintroduced into the cisterna magna and thus washes out through the lumbar needle the residual spinal anesthetic, so that the excess of spinal anesthetic is thus removed and the high effects of the anesthesia on the spinal cord begin to disappear within four or five minutes, gradually receding so that sensation and movement in the lower extremities usually return within twenty minutes. The operator is thus in possession of an exact means of determining the level of anesthesia desired and of preventing its diffusion to higher levels. The subsequent removal of spinal anesthetic by washing out the spinal canal through the lumbar needle both brings relief from the effects of the anesthetic and obviates the danger of further diffusion and spread to higher levels.

It will be found by use of the test described that complete anesthesia for pain and temperature may be produced up to the level

of the umbilicus (ninth thoracic segment), and that in spite of the fact that all the peripheral fibers contained within the sciatic and anterior crural nerves have supposedly entered the spinal cord below the twelfth thoracic segment, in the face of this demonstrable anesthesia, pain is still possible of production by deep pressure in the lower extremity, although the patient is not able to recognize superficial pin-prick, heat or cold. If the spinal anesthesia is raised to the third thoracic segment (the skin area in the axilla), this type of pressure pain entirely disappears and the patient is not able to appreciate superficial pain, heat or cold, or deep pressure and manipulation along the arteries, the bone or the painful areas involved in the extremity.

It is evident that pain fibers from the lower extremities reach the spinal cord through other pathways than the peripheral nerves to the lower extremities, probably following the arteries and the sympathetic system, and ultimately find their way into the upper thoracic cord between the third and fifth thoracic segments. That this type of deep pain referred to the lower extremities may find a high point of entry into the spinal cord has led to the supplementary operations of ganglionectomy and periarterial sympathectomy, when destruction of the peripheral nerves involved or corresponding roots failed to give relief. Anterolateral chordotomy (Spiller-Frazier operation) above the third thoracic segment offers the possibility of relief from such pain by including all the fibers from the lower extremity of the opposite side which have finally reached the spinal cord, crossed and begun to ascend toward the brain in the spinothalamic tract. Chordotomy formerly was performed at the fifth thoracic segment, but this has proved, in several instances in our experience, to be too low to include all fibers from the lower extremities from the opposite side of the body.

When spinal anesthesia is carried as high as the seventh cervical segment (paresthesias in the ulnar half of the hand, with demonstrable numbness), we have observed that the pain of atypical facial neuralgia immediately ceased, thus indicating the entry of pain fibers from the face, following the vascular and sympathetic system into the upper thoracic region. This may account for the various types of improvement reported as resulting from second thoracic ganglionectomy and combined pericarotid and lower cervical sympathectomy.

In order that pain may be appreciated by the patient, it is necessary that intact pathways from the diseased area reach the thalamus to be distributed to conscious perceptive levels of the cortex. The pathway carrying these fibers with sensation of pain and intense heat or cold in all probability lies within the spinothalamic tract as a separate bundle which comprises the anterolateral column of the spinal cord. This column is comprised of fibers that have entered the posterior roots of the opposite side, crossed over at the level of entry or within

two segments of this level and joined the anterolateral column directed toward the thalamus. Chordotomy, or section of the anterolateral columns (Spiller-Frazier operation), has demonstrated that it is possible to destroy the sense of pain, heat and cold on the opposite side of the body. It is evident that when pain persists after such an operation, either the section of the anterolateral columns was not complete or pain fibers from the part involved entered at levels higher than the point of surgical interruption.

Certain types of pain, such as causalgia, dull, throbbing, so-called vascular pain, have frequently remained in parts rendered superficially anesthetic by chordotomy, rhizotomy or block anesthesia to the test for pain, heat and cold. The complementary operations of sympathetic ganglionectomy and periarterial stripping have been devised in order to obtain relief from this vascular type of pain.

Formerly, chordotomy was popularly performed at the fifth thoracic segment, but, as demonstrable by our test, this level of the spinal cord has proved to be too low for the vascular pain fibers originating in the lower extremity. It seems apparent from these observations that final entry of all pain elements in the lower extremity is not complete until the third thoracic segment has been anesthetized. The visceral pain fibers probably enter even higher, but apparently have all found their way into the spinal cord below the level of the fifth cervical segment. Thus, the level of chordotomy selected will determine the success or failure as to partial or total obliteration of the pain elements arising from the parts involved.

Foerster and his associates [1] have shown that pain fibers on the blood vessels travel with the sympathetic fibers to enter the spinal cord at levels much higher than the peripheral nerve supply to the part under consideration. This is true especially of the lower extremity. In the head and neck, the vascular fibers follow the large vessels into the thorax and enter as low as the fifth thoracic segment. Thus, deep vascular pain of the face may persist after superficial anesthesia has been produced by section of the trigeminus, a fact which has been emphasized during the past five years in our studies on atypical facial neuralgia.

Kirschner [2] has recently described a method for obtaining spinal anesthesia at various levels which is somewhat similar to our own. In his method he does not use the cisternal needle but accomplishes his results by filling the caudal portion of the dural sac by direct injection

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2. Kirschner, M.: Spinal Zone Anaesthesia, Placed at Will and Dosage Individually Graded, Surg., Gynec. & Obst. **55**:317 (Sept.) 1932.

of air. An anesthetic solution which is not miscible with the cerebrospinal fluid separates out in a layer because it is lighter than the cerebrospinal fluid. The localization of the anesthesia is then determined by adding or diminishing the amount of air. With this method, however, he is unable to change or to graduate his anesthetic level once the solution has become fixed. To do so would necessitate the injection of a larger quantity of air, thus greatly increasing the intracranial pressure.

The possible disturbance which may arise from withdrawal of large amounts of fluid and the technical details required in manipulation of the patient to obtain the proper position of his fluid level are easily avoided in our method by means of a simple adjustment of the buret, as we have described. The method has proved to be controllable to the desired degree and offers no technical difficulty in the change of level of anesthesia if this is desired.

Observations with this test indicate that vascular types of pain arising in the face, the upper or the lower extremities are relieved when anesthesia of the spinal cord and roots has been obtained below the sixth cervical segment.

The exact level of entry of these pain fibers may be established by controlled spinal anesthesia, with objective and subjective observations as to the segment of the spinal cord which must be anesthetized in order to interrupt the pain of which the patient complains.

Chordotomy (section of the anterolateral columns of the spinal cord), when successfully accomplished above the determined level, we believe is capable of permanently abolishing the intractable pain of which the patient complains. The operations devised for relief of pain by means of rhizotomy, ganglionectomy and periarterial sympathectomy may find better analysis and indicate their appropriate application by means of this test. The value of fixation of spinal anesthesia at any desired level may offer surgical application in other cases in which high spinal anesthesia is required and absolute control necessitated.

PUNCTURE OF THE CISTERNA MAGNA

A MODIFICATION OF AYER'S METHOD, USED MORE THAN FIVE THOUSAND TIMES

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Since Ayer first described the technic for puncture of the cisterna magna [1] the procedure has been widely adopted; its advantages and indications have been discussed by numerous writers. Since November, 1929, cisternal puncture, with certain modifications of Ayer's method, has been carried out more than five thousand times at the Indianapolis City Hospital. The procedure was first adopted in treatment in a number of cases of basilar meningitis; later it was used in other cases.[2] in which many cerebrospinal drainages were necessary. Several patients had more than thirty cisternal punctures; many of them more than ten. Vonderahe and Haberman [3] reported a case of injury to the medulla and reemphasized the dangers of cisternal puncture and the need for preliminary practice on the cadaver. Since other accidents have been reported, perhaps the safeguards used on these patients merit a description.

TECHNIC

A needle of larger gage (16) that is not very flexible and has a small hilt is preferred, because it can be directed more accurately, a freer flow is insured, and the weight of the hilt will have less tendency to drag on the needle during the

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From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, and the Department of Neuropsychiatry, Indiana University School of Medicine.

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3. Vonderahe, A. R., and Haberman, F. C.: Injury of Medulla in Puncture of Cisterna Magna, Arch. Neurol. & Psychiat. **29**:166 (Jan.) 1933.

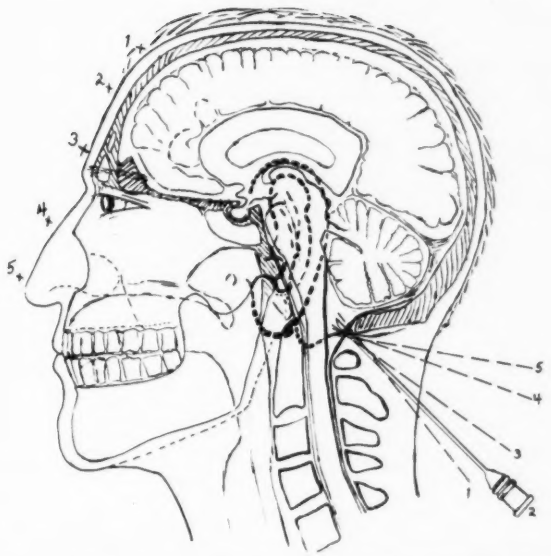

Fig. 1.—Composite diagram illustrating the relationships of external features to the position of the cisterna magna, medulla and cerebellum. At *2* the needle is pointed at *2x; 1, 3, 4* and *5* illustrate the margins of safety when the needle is inserted in these directions. The cisterna is at least 1 cm. deeper in directions *1* and *2* than at *4* and *5*.

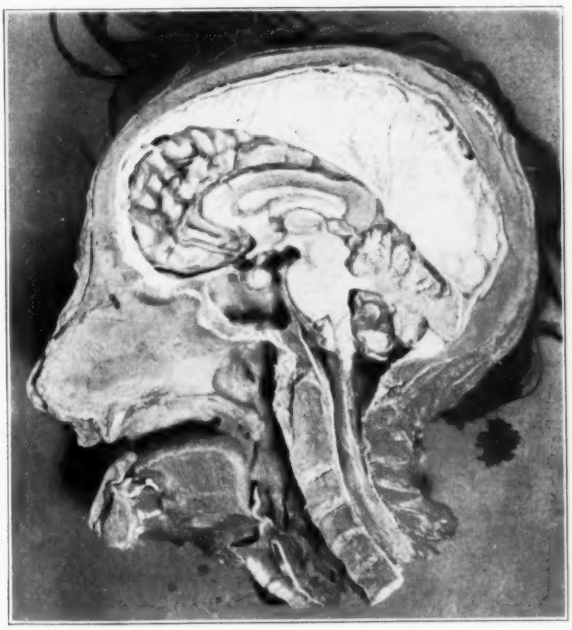

Fig. 2.—Photograph of an actual hemisection.

actual process of drainage. The needle should have a short, sharp bevel in order to allow entrance of the point without danger of the tip striking the medulla.

The patient is placed on the side, with the head on a pillow or pad of sufficient thickness to keep the head and the cervical and thoracic vertebrae in the same horizontal plane. The shoulders should be kept vertical and the head slightly flexed; however, patients in opisthotonos are allowed to maintain the position of their heads but are otherwise placed in the foregoing position. The position of the epistropheus is noted, and the finger is placed in the suboccipital triangle (felt between the occiput and epistropheus as the depression in which the finger cannot be moved horizontally or vertically without leaving it). The position of the posterior border of the mastoid process and its distance from the suboccipital triangle is estimated, and this is the approximate distance the needle will have to be inserted in order to reach the cisterna magna (fig. 1).

Iodine is applied over the suboccipital triangle, which has previously been clipped and shaved. A local anesthetic may first be instilled, although, when the

Fig. 3.—Insertion of the needle with the hands in a position to insure steadiness in performing the puncture.

puncture is to be repeated over a series of days, infiltration of the tissues frequently is not desirable because of the tendency to edema. With the patient's head facing straight forward, so that there is no twist of the neck to the right or left, the needle, with the bevel directed caudally so as to avoid skiving tissues from the occiput into its lumen, is inserted into the skin in the exact midline just at the upper border of the first spinous process. If the needle is started at a higher level one is apt to reach the cisterna with the needle pointed at the bridge of the nose, because the tissues and the bony configuration will prevent tilting. This direction gives 1 cm. less space for safety than if the needle is directed toward the normal hair line (fig. 1). If the needle is started in the exact midline at this point and directed at a point in the exact midline at the usual place for the hair line, one can in many cases slowly and steadily carry the needle into the cisterna magna without changing its course. However, the needle usually strikes the base of the occiput first, and, in either event, when the needle has been passed through the skin and outer ligaments, the stylet is removed. One then gradually pushes the needle toward the cisterna, never allowing the tip to point below the eyebrows and attempting to keep it pointed as nearly as possible toward the hair line.

In order to insure a steady and gradual movement of the needle and to avert its going too far when it passes through the dura, it is best to hold the needle with both index fingers and thumbs, keeping the remaining fingers against the patient's neck and head for support, as illustrated (fig. 3). This assures a steady, even pressure on the needle and prevents one from penetrating too deeply when the needle passes through the atlanto-occipital membrane. By this method the feel of passing through the dura (so essential when the stylet is left in) becomes less important, although it is still well to recognize it. *There are times when passage of the needle through the dura will not be felt even by one who has done many cisternal punctures.* As soon as the tip of the needle passes through the dura, spinal fluid appears, and with the larger needles even very purulent fluid appears at once.

Occasionally a flow will not be obtained (this occurred six times in more than five thousand punctures); then gaging the approximate distance by external features becomes important, and the feel of passing through the dura is useful. When one is in doubt, very gentle suction with an all glass syringe should be applied. When fluid does not appear after the proper distance has been traversed by the needle, and when it cannot be secured with a syringe, we should be inclined to call the tap a dry one and stop. A dry tap or complete failure has been experienced only twice, in both instances on patients who were moribund.

The required depth, as indicated by Ayer, is about from 4 to 4.5 cm., sometimes as low as 3 and as high as 6 cm.; however, frequently an unusually long occiput or an unusual muscular development makes the distance 7 cm., and occasionally the distance is 8 cm., or the whole length of the needle. Punctures have been performed repeatedly on the same patient; of the first fifty-two patients on whom the technic was used, eighteen had from one to ten, nineteen from eleven to twenty, ten from twenty-one to thirty, and five from thirty-one to thirty-five cisternal punctures.

When a syringe is attached to the needle in place, or when serum is introduced, one must guard against pushing the needle farther into the space; if, as occasionally happens, the needle is pulled out after some fluid has been withdrawn but before medication has been introduced or before drainage is complete, attempts to reinsert the needle are dangerous until the cerebrospinal fluid pressure is reestablished. This usually requires several hours; however, when necessary, lumbar puncture may be performed.

SUMMARY AND COMMENT

The important points are: (1) to locate the depression below the occiput, the mastoid process and the normal hair line; (2) to start and to keep the needle in the exact midline, directed at angles *1* and *2* in the diagram; (3) to keep the bevel directed caudally and to remove the stylet as soon as the needle has passed through the outer tissues; (4) to hold the needle with both thumbs and forefingers and to steady both hands against the neck and head of the patient, and (5) to start the needle low (just above the epistropheus).

In this series one case was seen at autopsy in which hemorrhage from the dura about the base of the brain may have been the result of the puncture. The cause of death was a purulent meningitis with multiple abscesses in the brain. While it is advisable to practice on

the cadaver, a false sense of security must be guarded against. With the aforementioned precautions and an understanding of the anatomic relationships, the method may be taught to physicians directly on the patient. Any one who lacks the patience to get his bearings correctly before inserting the needle or who lacks the mechanical skill or patience to insert the needle slowly and steadily should not attempt to perform a puncture of the cisterna magna.

The advantages of cisternal puncture are that it is much less painful than other procedures; it causes less discomfort after drainage; an ambulatory patient may soon be allowed up when only a few cubic centimeters are withdrawn; it is more feasible in cases with marked opisthotonos, and, as pointed out by others, it is valuable in cases of spinal block and in basilar meningitis. The necessity for frequent drainage of cerebrospinal fluid in the same patient may in itself be considered an indication for alternating the procedure with lumbar puncture.

EXPERIMENTAL VITAMIN (A, B_1, B_2 AND B COMPLEX) DEFICIENCY

HISTOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM

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AND

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After treating many patients suffering from the nervous complications of pernicious anemia with large doses of liver (vitamin A) over a long period and neither effecting improvement in the degenerations of the central nervous system nor preventing their onset,[1] we became skeptical of the effect of vitamin deficiency on the tissue of the central nervous system. Since both vitamin A and vitamin B depletion had been held responsible for degeneration of the central nervous system by various workers, we decided to reinvestigate the problem.

The discovery of a pellagra-preventing substance, vitamin B_2 or G, suggested to some workers that pernicious anemia, or possibly at least its neurologic manifestations, might be due to chronic vitamin deficiency. Koessler and Maurer thought that anemia in rats could be produced by depletion of vitamin A. Schaumann,[2] Hofmeister[3] and Woollard[4] produced paralysis of the extremities in rats depleted of vitamin B complex for short periods, and although paralysis was noted in some animals the central changes were mild and nonspecific, consisting in variable alterations in the anterior horn cells. Voegtlin and Lake[5] produced marked clinical symptoms, including paralysis and incoordination, in cats and dogs by depletion of vitamin B, but the symptoms

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cleared up in twelve hours after the administration of one dose of autolyzed yeast filtrate. Histologically, peripheral nerve demyelinization and scattered degeneration of central nerve fibers were found. Cowgill[6] produced spasticity in dogs depleted of vitamin B but reported no histologic studies.

Gildea, Kattwinkel and Castle[7] depleted fourteen dogs of vitamin B complex. The resulting progressive weakness, spastic paralysis, convulsions and coma were improved in a few hours by the administration of a few cubic centimeters of yeast extract. Histologic studies of the nervous system revealed only mild changes in the peripheral nerves, but irregularly appearing areas of almost complete demyelinization scattered diffusely throughout the central nervous system. Nuclear stains brought out only a moderate chromatolysis of Nissl's substance in the nerve cells of the cord and cortex. Zimmerman and Burack[8] repeated this work, and in their first report confirmed the results. Subsequently they concluded that the supposed patchy central degenerations were artefacts created by the faulty use of certain stains and were not revealed by other methods.

The effect of vitamin A depletion on the central nervous system has been studied recently by Mellanby.[9] In carefully controlled experiments on young dogs extending over a period of three or four months he demonstrated degenerative changes in the spinal cord with the Marchi method. Puppies fed a vitamin A-deficient diet showed clinical symptoms such as those noted in animals depleted of vitamin B complex. They became weak and ataxic, and terminal paralysis developed. Depleted animals that were given wheat germ or ergot showed much more severe symptoms and more severe histologic signs of degeneration. Vitamin A or carotene given to dogs in sufficient quantity prevented the destructive effect of ergot or wheat germ on the spinal cord. Mellanby concluded that degeneration of the cord is controlled by two factors, a positive harmful influence (toxin) and the absence of a defending mechanism (vitamin A). He applied his conclusions to the neurologic degeneration in pernicious anemia, multiple sclerosis and tabes dorsalis. These experiments may be criticized from the histologic point of view. The Marchi method, which is extremely treacherous and frequently

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leads to artefacts, was used almost to exclusion, and corroborative methods to demonstrate fat were not used. In most of the drawings of affected sections of the cord the granules were limited to the entire periphery of the sections. The time of depletion and the quantity of the granules revealed by the Marchi method did not seem to check. A decrease in the number of granules was reported in animals given vitamin A after an initial depletion and after the clinical symptoms had improved owing to other tracts taking over the lost function.

METHODS

Production of Vitamin B Deficiency in Rats.—The following basic conventional diets were used on the advice and with the assistance of Dr. Siegfried Maurer.

Vitamin B_2-Free Diet

	Per Cent
Egg albumin extracted five times and roasted	20.0
Minerals (Osborne and Mendel)	4.0
Dextrin	20.5
Starch	21.0
White corn-meal	20.0
Agar	2.0
Butter	10.0
Cod liver oil	2.5

Vitamin B Complex (B_1 and B_2)-Free Diet

	Per Cent
Egg albumin extracted five times and roasted	20.0
Minerals (Osborne and Mendel)	4.0
Dextrin	30.5
Starch	31.0
Agar	2.0
Butter	10.0
Cod liver oil	2.5

Vitamin B_1-Free Diet

	Per Cent
Egg albumin extracted five times and roasted	10.0
Minerals (Osborne and Mendel)	4.0
Dextrin	28.5
Starch	28.0
Agar	2.0
Butter	10.0
Yeast (Harris dried brewers' autoclaved for five hours)	15.0
Cod liver oil	2.5

The vitamin B_2-free diet contains adequate protein, carbohydrate, fats and minerals. The white corn-meal is the source of vitamin B_1; cod liver oil furnishes A and D, and white butter furnishes adequate A, D and E. The vitamin B complex-free diet is adequate, except that extracting and roasting the egg albumin has removed all the vitamins B_1 and B_2. Vitamin B_1 is removed from the third diet by the omission of the white corn-meal. Variations in these basic diets were

made by the addition of various vitamins as needed to bring the animals from a state of impending death and to produce recovery from the paralytic state. B_1 was added at these times in the form of wheat germ or white corn meal; B_2 from dried brewers' yeast autoclaved for five hours and B complex from dried brewers' yeast and Vegex.

Histologic Method.—All the animals were killed by ether inhalation. The brains, spinal cords and peripheral nerves were fixed in a dilute solution of formaldehyde. From representative areas of the central nervous system blocks were cut and stained for fat, glia, myelin sheaths, nerve fibers and cells by the methods of Herxheimer, Cajal, Spielmeyer, Bielschowsky and Nissl. The Marchi method was also employed on the spinal cords of the monkeys.

EXPERIMENTS

Vitamin B_1 and B_2 Deficiency.—Seven male rats from a mother fed a vitamin-rich diet before pregnancy were on the deficient diet for thirty-four days as nurslings, at the end of which period they were very small, weak and inactive and the average weight was 22 Gm. For the next two hundred and sixty-three days, these rats were on a diet adequate in vitamin B complex, on which they gained strength rapidly; at the end of this period their weights averaged 300 Gm. post mortem.

Seven rats in this group were from litters the mothers and grandmothers of which had been deprived of vitamin B_1 and B_2 for varying lengths of time before pregnancy (from twenty to thirty-five days). They were maintained on a B_1 and B_2 deficient diet for fifty days as nurslings and made only one-half the normal gain in weight. They were extremely weak and showed little activity. For the next two hundred and twenty-five days the rats were given a normal diet containing adequate vitamin B_1 and B_2, with recovery of strength and normal weight. A second period of B_1 and B_2 deficiency was then begun. Progressive weakness and loss of weight began at the end of the second week. The hair became scanty, and the skin appeared scaly and dry, with an occasional open sore. After three weeks the animals were listless, drowsy and inactive; if they were forced to move, the gait was stumbling, but there was no true paralysis. The rats were killed after from thirty to forty-two days of the deficiency diet and showed from 30 to 50 per cent loss of weight.

Vitamin B_1 Deficiency.—There were twenty-one rats in this group, and the routine was varied. Three male rats were given a vitamin B_1-deficient diet for one hundred and fifty-four days. At this time the average weight was 95 Gm. and the animals were extremely weak and inactive. They stumbled about, but showed no true paralysis. For the next one hundred and fifty days 2 Gm. of wheat germ and 10 per cent autoclaved yeast were added to the daily diet. The rats gained in strength and showed normal activity, but at the end of one hundred and fifty days of an adequate diet they were still somewhat underweight. The weights then averaged 200 Gm.

Nine male rats as nurslings were given a vitamin B_1-deficient diet for from fifty-one to fifty-five days. The average weights at the end of that period were 50 per cent below normal. The animals were weak and practically hairless; they were inactive and stumbled when forced to move. At this time 2 Gm. of wheat germ and autoclaved yeast were added to the diet. The animals revived, hair began to grow and strength returned. The animals were killed in from one hundred and sixty-eight to three hundred and sixty-nine days; the minimum normal weight had been reached in eight rats.

Two male rats were from a mother fed on a diet rich in vitamins and a B_1 and B_2 depleted grandmother (before pregnancy). These rats were kept on a B_1-deficient diet for seventy-eight days. They were runts, weighing, on an average, 38 Gm. at 70 days. Weakness and inactivity were more extreme than in the previous group, and the animals were hairless. It was doubtful if the rats could be maintained longer on the deficient diet, and they were given adequate diets, with the addition of vitamin B_1, for one hundred and ninety-four days. There was prompt return of strength and activity, and the minimum normal weight was reached.

Three rats were from a mother who had been given a vitamin B_1-deficient diet before pregnancy. These rats as nurslings were given a B_1-deficiency diet for one hundred and thirteen days. At the end of that time the average weight was 95 Gm. (50 per cent below the normal weight). These rats showed the extreme symptoms of the previous group. In addition, there were a few small open sores, and the skin was dry and scaly. At this time the animals were given minimum amounts of vitamin B_1. The amounts were changed frequently, and at no time did the rats arrive at normal weekly gains in weight. There was continued weakness, and the animals became drowsy and stupid; they moved only when stimulated, but there was no true paralysis. When the animals were sufficiently probed and annoyed they were able to cling to the sides of the cage. After one hundred and eighty-nine days of this procedure the rats were killed. The average weight was 200 Gm.

Three female rats as nurslings were given a vitamin B_1-deficient diet for fifty-two days. At the end of that period they were runts, weighing, on an average, 35 Gm. The hair was scanty, and the animals were weak; they moved in stumbling fashion when stimulated, but there was no true paralysis. At the end of fifty-two days the rats were given an adequate diet with vitamin B_1 added. Strength returned; the hair was heavy, and the animals were normally active at the end of two hundred and eighty-six days. The average weight was 270 Gm. At this time another period of vitamin B_1 deficiency was instituted. There was rapid loss of weight, weakness was progressive and rapid, and finally the rats dragged their hind legs when urged to walk. They stumbled blindly, but were still capable of clinging to the sides of the cage when sufficiently annoyed. The hair was scanty, but there were no sores. The loss of weight was from 38 to 48 per cent.

Vitamin B_2 Deficiency.—Six male rats as nurslings were given a vitamin B_1-deficient diet for fifty days. They became runts, with scanty hair and mild cutaneous lesions; they were extremely inactive and stumbled about the cage. At the end of this period it was necessary to give the animals a vitamin-rich diet for fourteen days to keep them alive. Strength increased, and the cutaneous lesions disappeared promptly. For the next one hundred and thirteen days a maintenance diet was given, with enough vitamin to insure a slow increase in weight. At the end of this period the hair was still scanty, but there were no sores. The average weight at the time of killing was 250 Gm., which is slightly below the normal weight for the male rats in this laboratory.

Six rats were placed on a vitamin B_2-deficient diet for thirty and twenty-three days respectively. They were weak, hairless runts, with scaly lesions of the skin. After this period vitamin B_2 was added to the diet. For the next one hundred and ninety-six days the rats gained weight and strength. At the end of this period, the animals were still somewhat underweight but showed normal activity. As adults they were again given a vitamin B_2-deficient diet. The males showed a loss of weight of from 33.3 to 54 per cent in one hundred and seventy days.

They became progressively weaker and for the last month walked with a peculiar hobbling gait, dragging the hindlegs and moving only when probed. There was no true paralysis, since with sufficient probing the rats could be forced to cling to the sides of the cages. The hair was again scanty, but there were no cutaneous lesions.

The females in this series as adults were kept on a vitamin B_2-deficient diet for from two hundred and eighty-five to three hundred days. They showed a 33 to 55 per cent loss of weight. The clinical symptoms were the same as those shown by the males of this group, except that cutaneous lesions were present. Three months before these rats were killed weakness was so extreme that they were given 2 Gm. of brewers' yeast in three doses during one week. There was prompt return of strength within twenty-four hours. The animals began to walk about at the end of the week and appeared to have normal strength. After three weeks, weakness was again apparent, and it became progressively worse day by day. Before the animals were killed they dragged the hindlegs and stumbled about the cage. In extreme excitement the animals could still be forced to cling to the cage weakly. In order to obtain photographs a piece of cheese was held above the rats. They became so excited that they balanced on the hindlegs without support. Considering the weakness exhibited in the cage, this exhibition of strength was extremely surprising.

Vitamin B_1 Deficiency in Nurslings and B_2 Deficiency in Adults.—Three male rats from a mother fed a vitamin B_1-deficient diet were placed on a vitamin B_1-deficient diet for fifty-one days as nurslings; as a result, they were runts, inactive and hairless, and huddled in a corner of the cage most of the time. For the next twenty days they were given a diet adequate in vitamins in order to keep them alive. At this time, aged 71 days, they weighed, on an average, only 60 Gm. and were so stupid that for twenty days even after an adequate diet they could not be run in the maze. After two hundred and thirty-three days of an adequate diet with complete vitamins they were still underweight. For the last one hundred and twenty-seven days of life they were placed on a vitamin B_2-deficient diet. There was rapid and progressive weakness. The rats lost weight rapidly and began to drag the hindlegs. They were very inactive and moved only when probed, but there was no true paralysis. The loss of weight was from 38 to 40 per cent.

Vitamin A Deficiency in Monkeys.—The dietary procedures in this experiment were carried out by Drs. Verder and Petren, whose report regarding the changes in intestinal flora will be published elsewhere. Seven Macacus rhesus monkeys were used, three of which were controls. The experimental monkeys were fed largely with polished rice and fresh butter. By aerating the butter, vitamin A was destroyed. The adequacy of vitamin A deficiency was controlled by feeding the same diet to rats, producing xerophthalmia and cachexia. The monkeys were kept on the diet for six and a half months; in the last month and a half they showed symptoms consisting of loss of weight, diarrhea, anorexia and cachexia. One monkey had generalized convulsions resembling those seen in tetany.

Histologic Changes.—The histologic observations may be summarized briefly, since they are largely negative. Although numerous sections from various parts of the central nervous system of all the animals, stained by various special methods, were carefully studied, no evidence of destruction of myelin sheaths, nerve fibers or ganglion cells was seen. With the Marchi, myelin sheath and fat stains no demyelinization was demonstrated either in animals depleted of vitamin in the period preceding death or in those depleted as nurslings and then given vitamin.

This statement holds true for the monkeys as well as for the rats. In all the animals rather mild and nonspecific alterations were found in some ganglion cells and in the endothelial lining of the smaller blood vessels.

SUMMARY AND COMMENT

The rats depleted of vitamins B_1, B_2 and B complex showed marked loss of weight and weakness. This in turn produced ataxia and incoordination that might well be interpreted as evidence of a serious degeneration of the central nervous system. However, one feeding of the depleted vitamin in our series and in those of other observers altered the weakness to such an extent that a more coordinate gait was possible. Furthermore, without the addition of vitamin to the diet, excitement caused the rats to climb the cages and balance on the hind-legs. Thus there was no clinical evidence of degeneration of the cord, for just as in pernicious anemia in man the severe weakness may imitate symptoms of serious involvement of the central nervous system. Rats depleted of vitamin B complex or of B_1 or B_2 showed no degeneration of the central nervous system. It seems fairly certain that Gildea, Kattwinkel and Castle were dealing with artefacts, and Zimmerman and Burack in their second report recognized that the changes reported in their original contribution were in reality artefacts. The conclusions of Castle and his co-workers that vitamin B deficiency is an etiologic factor in pernicious anemia does not hold, at least for the lesions in the cord.

Monkeys depleted of vitamin A showed no characteristic symptoms of involvement of the cord and no definite degeneration of the central nervous system. The work of Mellanby with the same type of vitamin deficiency in dogs requires rechecking by other histologic methods. The possibility that lack of vitamin A in the body enables certain wheat germs and ergotoxins to act on the central nervous system can hardly be related to human pernicious anemia. Vitamin A deficiency is rare, and its definite symptoms of xerophthalmia and night blindness are almost unheard of in this country. Furthermore, wheat germ, rye germ and ergotoxin are not frequently ingested, and yet combined degeneration of the cord, is extremely frequent.

Our animals were depleted as completely as was compatible with a long experimental period of depletion without premature death, and yet no symptoms of involvement of the cord or degeneration of the cord was found. Apparently vitamin deficiency does not produce degeneration of nerve fibers, although its effect on the ganglion cells of the central nervous system (central neuritis of Meyer) may, if the chronicity is great enough, endanger the existence of many nerve fibers (pellagra) and the vascular damage may eventually produce secondary ischemic effects.

CONCLUSIONS

1. Long-standing severe vitamin B_1, B_2 and B complex deficiency in rats causes no clinical symptoms or histologic changes in the central nervous system of a degenerative character save for mild nonspecific alterations in the ganglion cells and blood vessels.

2. Long-standing severe vitamin A deficiency causes no degeneration in the central nervous system of monkeys.

DISCUSSION

DR. ARTHUR WEIL, Chicago: I conducted some experiments on rats similar to those which Drs. Grinker and Kandel reported, but I did not publish them because of the relatively small number of animals used, twenty-four in all, which were divided into three groups of eight each. The first group was kept on a diet free from vitamin A. The second was fed a diet consisting of butter fat, casein, soluble starch and salt, and thus free from vitamin B, which was added to the diet of the first group in the form of yeast. The third group was fed the diet of the second group plus yeast.

The animals kept on the vitamin A-deficient diet survived more than three months. Six of the eight presented xerophthalmia rather late (within from five to ten weeks), but none of them showed any marked weakness of the hindlegs. In the second group, the clinical symptoms were more acute. Within from four to six weeks, six of these eight rats showed marked weakness of the hindlegs, which a few days later became paralyzed. Most of these rats died within forty-two days.

Serial sections were made of the brains and spinal cords of all sixteen rats, and of a number of normal rats also. No histologic changes pointing to disease of the central nervous system were found in the group on the vitamin A-deficient diet. In one rat in the second group marked degeneration was found by the Marchi method, extending over two or three segments and affecting isolated myelinated fibers of the lateral columns. No histologic change could explain the marked weakness and paralysis of the hindlegs of the other rats. Therefore, I was discouraged and discontinued the experiments.

The only explanation, perhaps, for the marked syndrome (weakness and finally paralysis of the hindlegs) in these experiments may be in the finding of primary lesions of the peripheral nerves by former investigators; or it may be that one is dealing with disease only of the muscle and not of the central nervous system. The rats which were used in my experiments weighed from 42 to 60 Gm. and were less than 20 days old.

DR. CHARLES DAVISON, New York: Experiments similar to those carried out by Dr. Grinker and Dr. Weil were made in our laboratory with all the vitamins (A, B, C, D and E). Some of these experiments have been completed. The only findings confirmatory of clinical neurologic signs in vitamin A and in vitamin B deficiency were dragging of the extremities and the appearance of convulsions or circular movements. The dragging of either the hindlimbs or the forelimbs in experiments with vitamin B deficiency came on about a week before death; in vitamin A deficiency the dragging of the extremities appeared a day or two before the animal died. I feel with Dr. Weil that the dragging of the extremities, especially in rats on a vitamin A-deficient diet, was due more to weakness than to actual neural changes, either in the peripheral nerves or in the spinal cord.

As to the changes in the central nervous system in these animals, I can say only that subarachnoid hemorrhages were noticed in some of the animals which had convulsions.

The rats deprived of vitamins A, B, C, D and E showed changes in the anterior horn cells and in some of the other ganglion cells of the central nervous system; these changes, however, were due to starvation or exhaustion and consisted essentially of vacuolation. Thus far I have been unable to confirm the presence of degenerations of the posterior and lateral columns and other neural changes, as described by Mellanby and others.

Dr. Weston Hurst, Princeton, N. J.: It may be of interest that at the Lister Institute, London, my associates and I have in the last two years examined many nervous systems from rats which have been subjected to vitamin B deficiency, and in no case have we been able to detect definite changes in the central nervous system. This was so even when the animals suffered from chronic deficiency; that is, when they showed symptoms of vitamin B deficiency and were given a small dose of vitamin enabling them to live for a few weeks, then showed symptoms and again were given a small dose of vitamin, with the result that they were kept in a state of vitamin B deficiency for many months.

Dr. Grinker has cast some doubt on the nature of the changes produced in Mellanby's dogs. There is no doubt that Mellanby produced definite lesions in the cord, because the degeneration was shown not only in sections stained by the Marchi method, which are notoriously unreliable, but also in sections stained with hematoxylin and scarlet red. The myelin sheaths, particularly around the periphery of the cord, had broken down and had undergone transformation to globules of neutral fat, leaving no doubt about the reality of the degeneration.

Dr. H. M. Zimmerman, New Haven, Conn.: About three years of work with these various deficiency diseases in conjunction with the department of physiologic chemistry of the Yale Medical School has shown my associates and me that the results obtained with the various animals that are used for studies of deficiency diseases cannot be compared. For example, it is difficult to produce any neurologic evidence of deficiency of vitamin B_1 B_2 or B complex in rats. These animals apparently store the vitamin B to such an extent that it is practically impossible to deplete them. It is possible to produce lesions of the skin, and recently some changes in the cornea have been described in rats on a vitamin B-deficient diet, but in the hands of many workers and also in our laboratory it has proved impossible to produce any lesions of the peripheral nerves or of the cord in rats with vitamin B complex deficiency.

On the other hand, after working with vitamin B deficiency in dogs, we have been able to show that marked peripheral polyneuritis of a purely degenerative type affects the myelin sheaths; if of sufficient duration this will lead to degeneration of the axis-cylinders also. We have been able to show, moreover, that dogs subsisting on a ration deficient in vitamin B_2 or G will show not only peripheral polyneuritis but marked degeneration of the posterior nerve roots and degeneration of the posterior columns of the spinal cord.

The degeneration is complete. It starts in the lumbar region and ascends into the medulla. The destruction is extensive and corresponds in almost all details to the changes that one sees in tabes dorsalis.

We have also been able to show, I think, that it is possible clinically to identify the lesion as a degeneration of the posterior columns by the fact that the dogs present not only paralysis of the posterior extremities, which is probably due to

the degeneration of the motor nerves, but ataxia and changes of the reflexes that are associated with degeneration of the posterior columns. These results will be published very shortly.

It is difficult, if not impossible, to produce a pure vitamin B_2 deficiency in dogs on the rations that are used in the usual experiments. It was only with the aid of Dr. Cogill and Dr. Mendel that we were able to devise a diet that is deficient in vitamin B_2 alone. The diets of natural foods that are usually employed are not deficient in vitamin B_2 alone.

As regards vitamin A deficiency, no one has mentioned that it is very difficult, as Mellanby pointed out, to produce vitamin A deficiency in an adult animal. The animals that Mellanby used were puppies and not adult dogs. Recently, Suzman, Muller and Ungley attempted to repeat Mellanby's experiments, using natural foods presumably deficient in vitamin A. They found that the adult dogs show all sorts of lesions except the xerophthalmia, which is supposedly characteristic of vitamin A deficiency. These animals showed no lesions in the spinal cord.

We repeated Mellanby's work, using an artificial diet which we believe is adequate in all essentials except for vitamin A, and showed that if young animals are employed, we can reproduce Mellanby's results perfectly in the rat. I do not doubt that Mellanby has produced degeneration of the spinal cord and peripheral nerves with a diet deficient in vitamin A.

However, it is not possible, I believe, to employ, as has been done in past experiments, diets of natural foods which are presumably deficient in one or another single vitamin. It is highly important, as has been pointed out in the paper that Dr. Burack and I presented, to employ artificial rations which one knows to be satisfactory as far as protein, fat and carbohydrates are concerned, and which are supplemented by all the vitamins except the one that is to be used for study.

Dr. Lewis D. Stevenson, New York: Last winter, in order to get some specimens of peripheral neuritis for class demonstration, my associates and I in our laboratory fed some chickens on polished rice, and we produced typical peripheral neuritis. Although we found no loss of myelin in the spinal cord, we found a great increase in the number of microglia cells, so I think some change was going on in the spinal cord, although it had not arrived at the stage of breaking down the myelin sheaths.

Dr. Roy R. Grinker, Chicago: The weakness that Dr. Weil spoke of, I believe, can be attributed not alone to a morphologic change within the peripheral nerves but to some functional disturbance which can easily be improved within a few hours by the addition of a small amount of vitamin. It is interesting also that one may expect a very rapid regeneration, even though a morphologic change takes place, since, as has already been shown, the first changes occur in the nerve endings in the muscle.

The question as to whether one is dealing with degenerations in the central nervous system or not as the result of vitamin B deficiency seems to depend specifically on the diet, and on the animal used. We used an artificial diet, specially prepared by Dr. Siegfried Maurer, who has been working on vitamin B deficiency for some time. This diet does not contain natural foods and it is made essentially to exclude one particular type of vitamin. As a result of this, we are not starving our animals, but we are depleting them of a single vitamin. These animals show the typical symptoms of vitamin deficiency—symptoms which can be improved very rapidly by the simple addition of the one vitamin. Furthermore, the apparent ataxia and paralysis rapidly disappear. If one studies the animals

clinically very carefully, one can make the animals which apparently are ataxic do stunts, such as climbing cages and romping around, without any evidence of a neurologic defect by producing excitement from the sight of food.

The question as to the age of the animals is important. As I mentioned before, we were using very young animals; in fact, we were producing depletions through a series of three generations, and in the third generation the depletion was produced in nurslings. I believe that Dr. Zimmerman meant to give the impression, not that vitamin B deficiency could not be produced in rats, but rather that no changes in the central nervous system could be effected by such deficiency. The changes in the posterior column which was produced in dogs may be secondary to damage of the sensory portion of the peripheral nerves.

As far as the changes in the central nervous system are concerned, I think that one must be very cautious in the interpretation of another person's methods, but certainly the illustrations in papers that have designated deficiencies as producing such changes are not convincing.

SEDIMENTATION RATE OF THE BLOOD IN SCHIZOPHRENIA

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As a part of a general investigation of the organic functions in schizophrenia (Hoskins and others [1]), a study was undertaken of the sedimentation rate of erythrocytes. For the past decade this reaction has been recognized as a sensitive index of damage to tissue or of infection. The elaborate series of tests utilized seemed to assure the detection of complicating physical illnesses. With the elimination from the study, of patients with other diseases, it was thought that if any elevation of the sedimentation rate was found, it could be attributed to factors inherent in the psychosis.

An examination of the literature on the application of this test in schizophrenia shows a marked lack of consistency of results. The sedimentation rate has been found to be retarded,[2] normal [3] or increased.[4] It has been noted to vary during different stages of the illness, having a normal value in the initial period [5] and an elevated rate in the deteriorated phase.[6] A rapid fall of cells has been frequently observed in excited or catatonic patients.[7] The increase in

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rate has been generally considered to be of a "moderate" degree,[8] although the lack of quantitative specificity of this reaction makes this statement of little value. Owing to essential differences in method, direct comparison of test results of various investigators is difficult. One investigation only, that of Stephenson,[9] whose technic is the same as that utilized in the present study, permits of legitimate comparison with our findings. Stephenson found that in 150 male schizophrenic patients with no apparent physical disease or infection, 60 per cent had elevated rates of sedimentation, and that these rates did not depend on the type of dementia praecox, on the amount of mental deterioration present or on the physical condition.

METHOD OF STUDY

In the general study,[1] the examination was sufficiently elaborate to detect pathologic processes so that persons so affected might be eliminated from further investigation. Patients with minor intercurrent infections were not excluded, however, and consequently we could attribute abnormal rates to the psychosis only in the absence of all assignable causes. The number of patients is small, only 47, but the group was studied so intensively that the results are thought to be reliable. Three determinations were made on these male schizophrenic patients at intervals of three months, in the last week of a study period extending over four weeks. To check the results, the sedimentation rates were also determined in 50 normal men, these including members of the staff, medical students and employees. While these subjects were not put through the rigid investigation undergone by the patients to exclude infectious processes, and while, undoubtedly, a small percentage suffered from minor ailments, they were all healthy and active, and probably represented a fair sample of the general community. Only a single determination on each was made in this group.

The sample of blood was taken in the morning, under nonfasting conditions, from the median basilic vein, with the aid of a tourniquet, 3 cc. being drawn into a clean, dry syringe and deposited in a test tube coated with dried heparin by the method of Plass and Rourke.[10] The blood was transferred a short time later, after having been shaken for two minutes, to sedimentation tubes[10] supported vertically in a special rack, and readings were made of the rate of fall of the red cells every ten minutes for three hours. The temperature of the room varied between 21 and 24 C. Following the readings the blood was centrifugated for thirty minutes at a speed of 3,000 revolutions per minute, and the percentage of cells by volume was noted. The sinking velocity of the red cells was then calculated from the rate of fall during the constant period of sedimentation, by the method of Rourke and Ernstene,[11] and corrected in accordance with their technic

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for deviation from normal value for the hematocrit reading. A so-called "corrected sedimentation index" was obtained which represented the rate of fall of the red cells with the effect of anemia eliminated, thus reflecting more truly the influence of abnormal processes. The normal values for this technic range between 0.08 and 0.35 mm. per minute. The material from the present study has been analyzed to investigate the relationship between the percentage of cells by volume and the uncorrected sedimentation rate. In a later article[12] it will be shown that the variability of the hematocrit reading is so great that any exact relationship with the sedimentation rate is not obtainable, and that in nonanemic cases the correction factor may be disregarded. In addition, the maximum normal value has been determined as 0.40 mm. per minute when the hematocrit correction is not made. However, for purposes of comparison, Rourke and Ernstene's criteria will be utilized throughout this paper unless otherwise specified.

Preliminary to the main investigation of the sedimentation rate, a few special studies were made. The first of these was on the effect on the sedimentation rate of venous stasis as applied in the taking of a sample of blood. Plass and Rourke[13] found that the sedimentation rate is increased by prolonged stasis, and other experimenters recommend that venous stasis be avoided in taking blood for this test. As the use of a tourniquet is sometimes required with uncooperative patients, it was thought desirable to determine its effect on the sedimentation rate. Accordingly, in 10 patients samples of blood were first obtained without stasis, and then, as soon as bleeding had stopped, from the same vein after the application of a tourniquet for from thirty to sixty seconds. The effect on the rate was slight and inconsistent. The change in sinking velocity due to stasis varied from 0.09 mm. per minute slower to 0.12 mm. per minute faster, the net difference being 0.004 mm. per minute slower, and the average difference, irrespective of direction, 0.05 per minute. In view of these extremely slight variations it seems probable that the use of a tourniquet has not biased the results.

As many of the studies of the general project[1] were conducted under "basal" conditions, it was deemed necessary to investigate the effect of digestion and of mild activity on the sedimentation rate to ascertain the effect such factors might have on the variability of the reaction. Accordingly, in 21 patients, samples of blood were obtained under fasting conditions at 8:30 a. m.; immediately after breakfast, at 9:30 a. m.; at the height of digestion, at 11:30 a. m.; and in the middle of the afternoon, at 3:30 p. m. Between the tests the patient's activities were not varied from their accustomed routine. The results were as follows: as compared with the sedimentation indexes for 8:30 a. m., the velocities for 9:30 a. m. were, on the average, 0.013 mm. per minute slower; the rates for 11:30 a. m. were slightly faster, on the average, 0.005 mm. per minute, and the values for 3:30 p. m. were exactly the same. It should be noted that not only the mean differences but also the individual variations were very slight, so much so as to be entirely insignificant. It was evident, therefore, that the diurnal variation of the sedimentation rate in patients with schizophrenia was so small as to be entirely negligible in its influence on the reaction. This finding confirms the observations of Plass and Rourke[10] in normal persons.

A brief study was made of a group of severely infected patients to determine the sensitivity of the sedimentation reaction and the approximate range of values

12. Jellinek, E. M., and Freeman, H.: Unpublished data.

13. Plass, E. D., and Rourke, M. D.: The Effect of Venous Stasis on the Proteins of Blood Plasma and on the Rate of Sedimentation of the Red Blood Corpuscles, J. Lab. & Clin. Med. **12**:735 (May) 1927.

under such conditions. Twenty patients were selected, 9 with far advanced pulmonary tuberculosis, 3 with acute infections of the upper respiratory tract, 2 with bronchopneumonia (1 of these was moribund), 2 with suppurative tenosynovitis, 2 with subcutaneous abcesses, 1 with facial erysipelas and 1 with chronic mastoiditis. Of these patients, 17 had abnormal rates of sedimentation, ranging as high as 1.60 and averaging 1.1 mm. per minute. Three patients, 1 with mastoiditis, 1 with an acute infection of the upper respiratory tract, and 1 with bronchopneumonia (from which he died within twenty-four hours), had normal sedimentation rates. It is evident that, although in cases of frank infection the sedimentation rate commonly becomes elevated far above the normal range, in a small percentage of cases it may fail to indicate the presence of such a condition. A similar observation has been made by Pinner, Knowlton and Kelly [14] in advanced cases of pulmonary tuberculosis. The paradoxical depression of the sedimentation rate in a moribund person has also been found by Townsend and Roger [15] and by Cutler; [16] the latter attributed it to a "destruction of the forces" that cause the reaction.

TABLE 1.—*Distribution of Sedimentation Rates in Schizophrenic and in Normal Subjects* *

	No.	Minimum, Mm./Min.	Maximum, Mm./Min.	Range, Mm./Min.	Mean and σ m, Mm./Min.	S. D. and σ s. d., Mm./Min.	C. V., per Cent
Corrected Sedimentation Index							
Period I.....	47	0.02	0.60	0.58	0.22 ± 0.01	0.14 ± 0.01	67
Period II.....	47	0.01	1.02	1.01	0.24 ± 0.03	0.19 ± 0.01	79
Period III.....	46	0.03	0.73	0.70	0.29 ± 0.03	0.16 ± 0.01	54
Normal group..	50	0.01	0.99	0.98	0.26 ± 0.03	0.21 ± 0.01	80
Uncorrected Sedimentation Index							
Period I.....	47	0.05	0.66	0.61	0.22 ± 0.02	0.13 ± 0.01	59
Period II.....	47	0.03	0.65	0.62	0.27 ± 0.03	0.18 ± 0.02	67
Period III.....	46	0.04	0.60	0.56	0.27 ± 0.02	0.15 ± 0.02	56
Normal group..	50	0.01	0.98	0.97	0.20 ± 0.03	0.18 ± 0.02	90

* In this table σ m = standard error of the mean; S. D. = standard deviation; σ s. d. = standard error of the standard deviation; C. V. = coefficient of variation.

RESULTS

The results of our investigation are summarized in table 1. The average values in all three periods for the patients and also for the control group fall below the normal maximum, as determined by Rourke and Ernstene,[11] in both the corrected and the uncorrected figures. The lack of correction for hematocrit reading has little effect on the means, as the second part of table 1 shows. There is a slight elevation of the mean sedimentation rate in the second and third periods, not, however, of any significance statistically. More detailed analysis

14. Pinner, M.; Knowlton, K., and Kelly, R. G.: The Sedimentation Rate of Erythrocytes: Its Relation to Fibrin Value and Cholesterol Content and Its Application in Tuberculosis, Arch. Path. **5**:810 (May) 1928.

15. Townsend, C. D., and Roger, H. B.: A Contribution to the Study of the Erythrocyte Sedimentation Reaction, J. Lab. & Clin. Med. **13**:819 (June) 1928.

16. Cutler, J.: The Graphic Presentation of the Blood Sedimentation Test: A Study in Pulmonary Tuberculosis, Am. J. M. Sc. **171**:882, 1926.

of the figures reveals that with the correction factor utilized, 20 per cent of the control group present abnormal rates, and of the patients 19 per cent in the first period, 23 per cent in the second and 28 per cent in the last. With the hematocrit correction disregarded, and assuming a normal maximum of 0.40 mm. per minute,[12] the following percentage of pathologic rates is observed: in the controls, 10; in the patient's first period, 8.5; in the second, 21, and in the third, 20. The incidence of 10 per cent rather than 20 per cent of pathologic rates in normal subjects seems to indicate that the latter technic provides a more reasonable type of criterion. The elevated rates are probably due for the most part to the presence of mild chronic respiratory infections, which are so prevalent in the New England climate. Among the patients, of the 32 with abnormal readings (above 0.35 mm. per minute) in the entire study, possible causes for the elevation of the rate, ranging from infections of the upper respiratory tract to indolent

TABLE 2.—*The Sedimentation Rate in the Subclasses of Schizophrenia*

Subtype	Number of Observations	Mean, Mm./Min.
Catatonic	19	0.23
Paranoid	23	0.25
Hebephrenic	32	0.28
Simple	6	0.20
Indeterminate	25	0.29
Unclassified	16	0.25
Mixed	13	0.26

ulcers, were obtained in 20. The majority of these cases occurred in the later test periods which extended through the winter and spring months. The higher incidence of abnormal rates among the patients is probably to be attributed to the greater opportunity for transference of infections within closed wards. In the other 12, occurring in 6 patients, a definite cause for the elevation of the rate could not be ascertained. This figure constitutes 9.3 per cent of the total number of examinations and is probably fairly comparable to the percentage of normal persons in whom it would be difficult to determine a basis for a high sedimentation rate.

We cannot, therefore, say that the group of patients with schizophrenia shows, on the whole, a significantly higher rate than the group of normal controls, and consequently we cannot conclude that schizophrenia is characterized by an elevation of the sedimentation rate.

COMMENT

Since the literature is so replete with findings of differences in the sedimentation rates among the subtypes of schizophrenia, it seemed desirable to determine whether this finding obtained in our group of

patients. In table 2, the mean values for the subclasses throughout the three periods are combined into a single measure. An explanation is necessary for some of the terminology used. "Mixed" refers to patients showing well defined symptoms of two or more types; "unclassified" implies a lack of cleancut symptomatology by which a case could be placed in any one class. The term "indeterminate" includes the later deteriorated stages of schizophrenia, in which the general thought content and behavior are vague and apparently affectless.

The differences between the sedimentation rates among the various subclasses are so slight as to be of no significance. Neither the "catatonic" nor the "indeterminate" patients showed the abnormal values so frequently ascribed to them in the literature. The group is, of course, too small to be conclusive, but our results coupled with Stephenson's findings on a larger group would seem to justify the conclusion that no significant difference in the sedimentation reaction exists among the subtypes of schizophrenia.

An effect of age on the sedimentation reaction has been noted by many observers. Greisheimer, Johnson and Ryan [17] found a definite elevation of the rate with an increase in years. Lasch [18] and Löw-Beer [19] similarly observed an increased rate in elderly, noninfected persons. In the present group of patients, the ages ranged from 18 to 45, with a mean of 31½ years. In the normal group, the figures were similar. In neither group was any correlation whatever found with age, although this may possibly be due to the narrowness of the age zone.

The sedimentation rate was also plotted against the period of hospitalization of the patients, which varied from two months to twenty-one years, the mean being five and one-half years. No relationship was found. However, the duration of hospitalization is a complex variable, containing, as it does, elements of chronological age and to a certain extent probably, of mental deterioration. As the sedimentation reaction was not affected by either process, the lack of correlation may in part have been due to the inclusion of such factors.

No correlation was found with blood cholesterol, blood sugar, nonprotein nitrogen, blood volume, basal metabolic rates or blood gases

17. Greisheimer, E. M.; Johnson, O. H., and Ryan, M.: The Relationship Between Sedimentation Index and Fibrin Content in Relatively Normal Individuals, Am. J. M. Sc. **177**:816 (June) 1929.

18. Lasch, F.: Untersuchungen über die Ursache der beschleunigten Blutsenkungsgeschwindigkeit im höheren Alter, Wien. Arch. f. inn. Med. **22**:155, 1931; abstr., Chem. Abstr. **26**:1655, 1932.

19. Löw-Beer, L.: Die Blutsenkungsgeschwindigkeit im höheren Alter, Klin. Wchnschr. **8**:1909 (Oct. 8) 1929.

(with the exception of the venous carbon dioxide). As from a week to ten days intervened between these various determinations and the observation of the sedimentation rates, no conclusion can be drawn from the lack of correlation in our findings. The variability of some of these processes in schizophrenia is so marked that only by means of simultaneous tests can it be determined whether correlation is present or absent. With regard to the venous carbon dioxide, relatively less variation is found,[20] and here a mild positive correlation was established of 0.30 ± 0.13; this is not sufficiently significant, however, to be conclusive. The positivity of the correlation is not in agreement either with Stephenson's [9] findings of a similarity in the sedimentation rates of arterial and venous blood or with the diminution in the sinking velocity obtained by increasing the carbon dioxide content of the blood.[21] It is, however, in accordance with the results of Plass and Rourke [13] in which the increase in venous carbon dioxide resulting from stasis was paralleled by a rise in the sedimentation rate. The cause for this interrelationship has not been determined in the present experiment and must remain a problem for the future.

The relationship between the number of the red cells and the sedimentation rate has been noted by many investigators (Hubbard and Geiger,[22] Gram,[23] Greisheimer, Ryan and Johnson,[24] and Walton [25]) who have proposed various formulas to compensate for the influence of the diminution in the red cell count. On the other hand, Rubin [26] found that between values of 4,000,000 and 5,000,000 red cells per cubic millimeter this factor was of no appreciable importance. This last observation has been confirmed by our results. In this study no correlation was found with the red cell count. The erythrocyte count in the patients varied from 4,000,000 to 6,000,000, with a mean of 4,900,000. These examinations were made from seven to fourteen days before the sedimentation rate was determined, and it is possible that the variability

20. Looney, J. M., and Freeman, H.: Unpublished data.

21. Ito, W.: Ueber den Einfluss der Blutgase (des Sauerstoffs und der Kohlensäure) auf die Senkungsgeschwindigkeit der Erythrozyten, Tohoku J. Exper. Med. **5**:139, 1924.

22. Hubbard, R. S., and Geiger, H. B.: Anaemia as a Factor in the Sedimentation Time of Erythrocytes, J. Lab. & Clin. Med. **13**:322 (Jan.) 1928.

23. Gram, H. C.: The Results of a New Method for Determining the Fibrin-Percentage in Blood and Plasma, Acta med. Scandinav. **56**:107, 1922.

24. Greisheimer, E. M.; Ryan, M., and Johnson, O. H.: The Relationship Between Cell Count and Sedimentation Index, Am. J. Physiol. **89**:170 (June) 1929.

25. Walton, A. C. R.: The Corrected Erythrocyte Sedimentation Test, J. Lab. & Clin. Med. **18**:711 (April) 1933.

26. Rubin, E. H.: The Relation of the Erythrocyte Sedimentation Reaction to the Ability of Flocculation of the Plasma and Serum, Arch. Int. Med. **37**:848 (June) 1926.

of the number of red cells in such a lapse of time may have prevented the appearance of any trend. To check this factor more closely, in 20 cases the red cell counts were made within a few minutes of the observation of the sedimentation rate, but still no relationship was found. We conclude, therefore, that within essentially normal limits the number of the red cells plays no important rôle in the speed of the sedimentation reaction. Nor is this to be wondered at when one considers the marked variability found by Sabin [27] in the red cell count during a single day—as high as 1,000,000 cells per cubic millimeter—contrasted with the lack of diurnal variation of the sedimentation rate.

A similar conclusion was reached in regard to hemoglobin. This was determined with a Hayden-Hausser hemoglobinometer and fell within normal limits, the average being 15.3 Gm. A relationship with the sedimentation rate could not be established. The lack of correlation of the latter with the percentage of red cells by volume or hematocrit reading will be discussed in another paper.[12]

One would expect the total leukocyte count, as an index of infection, to bear some relationship to the sedimentation rate. In disease there is a rough parallelism [28] though, owing possibly to the greater variability in the number of leukocytes,[29] the picture is sometimes contradictory.[30] In normal subjects, Greisheimer and his co-workers [24] found no correlation between the sedimentation rate and the total leukocyte count, or the percentage of neutrophils or of lymphocytes. Our findings in the general study were similar. In the 20 cases of almost simultaneous examinations of the blood and determination of the sedimentation rate a positive correlation coefficient of 0.54 ± 0.19 was obtained between the uncorrected sedimentation rate and the leukocyte count. The relationship between the two variables is to be ascribed probably not to an interdependence of one factor on the other, but rather to complex physiochemical processes which cause changes simultaneously in the number of leukocytes and in the sedimentation rate of the erythrocytes.

As three tests were performed on each patient over a period of seven months, the data present an opportunity to determine the degree of variability of the sedimentation rate in different persons. The uncorrected sedimentation rates for each period were plotted against each other (chart); in each case the readings fell within a narrow zone

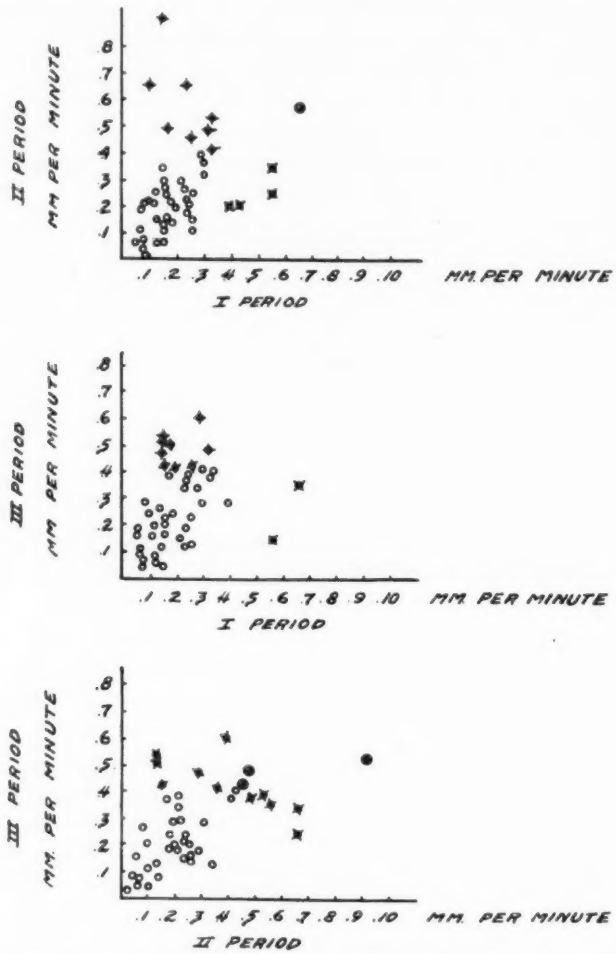
27. Sabin, F. R.: Bone Marrow, Physiol. Rev. **8**:226, 1928.

28. Ernstene, A. C.: Erythrocyte Sedimentation Plasma Fibrinogen, and Leukocytosis as Indices of Rheumatic Infection, Am. J. M. Sc. **180**:12 (July) 1930.

29. Garrey, W. E., and Butler, V.: Physiological Leucocytosis, Am. J. Physiol. **90**:355 (Oct.) 1929.

30. Heimann, F.: Blutkörperchensenkung und Leukocyten, Zentralbl. f. Gynäk. **56**:1378, 1932.

until the point 0.40 mm. was reached, after which there was a marked scatter, indicating, probably, the influence of some extraneous factor, such as infection. As it has been assumed that 0.40 mm. is the upper limit of normality under this technic, the rates below this level were



Self-correlation of uncorrected rates of sedimentation for three periods. The circles designate normal rates; the crosses and circles, pathologic rates in one period; the double circles, pathologic rates in two periods.

examined, and positive coefficients of 0.44 ± 0.14, 0.48 ± 0.15 and 0.47 ± 0.15 were found between the first and second, the first and third and the second and third periods, respectively. These values are not high, but for physiologic variables, they exhibit fair consistency. Analysis of the individual rates (table 3) showed that of the 37 patients who

had uncorrected rates below 0.40 mm. per minute throughout the seven months, the sinking velocity of the red cells exhibited a mean range of 0.09 mm. per minute, with a variation of not more than 0.15 mm. per minute in 95 per cent of the tests. It is evident therefore that although changes in the sedimentation rate do take place at intervals of three months such variation moves within a very limited range so that the sedimentation rate of an individual (exclusive of infectious factors) may be said to be characteristic of that person.

In a previous paragraph it was stated that the purpose of this investigation was the utilization of the sedimentation reaction as a sensitive detector in the hope of finding an organic pathologic process in the background of schizophrenia. The study was controlled, first, by the elimination of patients presenting overt symptoms or signs of infection and, second, by an analysis of the reaction in a numerically com-

TABLE 3.—*Individual Ranges of Uncorrected Sedimentation Rates Over Seven Months*

Range, Mm./Min.	Per Cent of Occurrence
0 -0.05	33
0.06-0.10	24
0.11-0.15	38
0.16-0.20	5
	Mm./Min.
Mean	0.09 ± 0.008
Standard deviation	0.049 ± 0.006

parable group of normal persons. The results were practically negative in that the reaction showed essentially the same distribution of values in the patients as in the controls. In one sense this is of some significance as confirming the rigidity of the standard of examination.

The dissimilarity of the findings in this study with those of other investigators is difficult to explain. Variations of technic, when well controlled, should be of slight importance in the final evaluation of results. In the case of Stephenson,[9] however, whose methods were identical with those used in the present study and who found 60 per cent of abnormal rates as compared with our 20 per cent, even this factor is eliminated. The inference may be drawn, however, that the pathologic rates, in some cases at least, may have been due to the presence of toxic or infectious processes of obscure origin. The normality of the findings in the present study do not, of course, disprove the possibility of a pathologic process in schizophrenia. Its determination, however, must await the discovery of newer and more sensitive methods of investigation.

SUMMARY

In a study of the sedimentation rate by the method of Rourke and Ernstene in 50 normal and 47 schizophrenic male subjects selected on the basis of relative freedom from detectable infectious processes, the following observations were made:

1. In the normal subjects, the mean sedimentation rate was 0.26 mm. per minute. Of these, 20 per cent had rates more rapid than the conventional normal limit of 0.35 mm. per minute.

2. In the cases of schizophrenic subjects, three tests were made at intervals of three months, covering a period of seven months. For these three series, the mean values for the sedimentation rates were 0.22, 0.24 and 0.29 mm. per minute. These were all within normal limits and were not significantly different from one another. In the first period of study, 19 per cent had abnormally rapid rates; in the second, 23 per cent, and in the third, 28 per cent. Of the 32 instances of pathologic rates, causes in the form of minor ailments could be detected in 20.

3. The subclasses of schizophrenia showed no significant differences in the sedimentation reaction.

4. In noninfected subjects a mean variation of only 0.09 mm. per minute in the sedimentation rate occurred over a period of seven months, and seemed to be characteristic of each person.

5. There was no diurnal variation of the sedimentation reaction.

6. Temporary venous stasis had no effect on the sedimentation rate.

7. No correlation could be detected between the age or period of hospitalization and the sedimentation rate.

CONCLUSION

Infection being excluded, schizophrenia is characterized by a normal sedimentation rate of the blood.

RELATIONSHIP OF ARTERIAL BLOOD PRESSURE TO CEREBROSPINAL FLUID PRESSURE IN MAN

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The relationship of arterial blood pressure to cerebrospinal fluid pressure has been discussed in an article published by Fremont-Smith and Kubie.[1] It was pointed out that the cerebrospinal fluid pressure was practically unaffected by variations in the arterial pressure, and that the arterial pressure was unaffected by an increase in the intracranial pressure unless the latter approached the level of the diastolic blood pressure. These conclusions were based almost wholly on experiments with animals, especially those of Becht,[2] Cushing[3] and Eyster, Burrows and Essick,[4] and have been confirmed by Wolff and Forbes.[5] Shelburne, Blain and O'Hare,[6] in a recent article, reviewed the scant clinical literature on this subject and reported the cerebrospinal fluid pressure in 50 cases of vascular hypertension. Their results will be discussed later.

There has been no clinical study of a large series of cases in which the cerebrospinal fluid pressure and the arterial blood pressure have been correlated. It is the purpose of this study, therefore, to present

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1. Fremont-Smith, F., and Kubie, L. S.: The Intracranial Pressure in Health and Disease, Association for Research in Nervous and Mental Disease, Baltimore, Williams & Wilkins Company, 1929, vol. 8, chap. 7.

2. Becht, F. C.: Am. J. Physiol. **51**:1, 1920.

3. Cushing, H.: Bull. Johns Hopkins Hosp. **12**:290, 1901; Am. J. M. Sc. **124**:375, 1902; Mitt. a. d. Grenzgeb. d. Med. u. Chir. **9**:773, 1902.

4. Eyster, J. A. E.; Burrows, M. T., and Essick, C. R.: J. Exper. Med. **11**:489, 1909.

5. Wolff, H. G., and Forbes, H. S.: The Cerebral Circulation, Arch. Neurol. & Psychiat. **20**:1035 (Nov.) 1928.

6. Shelburne, S. A.; Blain, D., and O'Hare, J. P.: The Spinal Fluid in Hypertension, J. Clin. Investigation **11**:489 (May) 1932.

such data for 1,606 cases, and to show that the conclusions reached in experiments with animals hold good for man.

For the purpose of this study the cases were divided into three groups: 1. One thousand four hundred and eighteen cases of various medical and neurologic diseases. These were selected in order to reflect any possible relationship between arterial blood pressure and cerebrospinal fluid pressure. Therefore, all cases were eliminated in which there might be an abnormal cerebrospinal fluid pressure due to some other factor. 2. One hundred and twenty-two cases of a high cerebrospinal fluid pressure due to diseases which produce, or are commonly associated with, increased intracranial pressure. 3. Sixty-six cases of uremia or congestive heart failure.

METHODS

The 1,606 cases here reported were studied in the various services at the Boston City Hospital during the past five years. The lumbar punctures and determinations of blood pressure were done by us and by the various members of the house staff during that period. The lumbar punctures were performed with the patient in the lateral recumbent position, and the cerebrospinal fluid pressure was measured with the Fremont-Smith modification of the Ayer water manometer. All cases in which there was technical difficulty in the performance of the lumbar puncture, such as lack of cooperation of the patient and poor relaxation, were discarded. In the great majority of the cases the determinations of blood pressure and the readings of cerebrospinal fluid pressure were made on the same day. A few cases showing a normal blood pressure and normal cerebrospinal fluid pressure in which there was an interval of one or more days between the two determinations are included. Cases showing a high cerebrospinal fluid pressure or a high blood pressure were excluded unless the determination of the two pressures was made on the same day, except in the cases showing high blood pressure in which frequent determinations revealed the blood pressure to be relatively constant.

RESULTS

Group I: Influence of Systolic Blood Pressure on Cerebrospinal Fluid Pressure.—The 1,418 cases in this group were chosen to reflect any definite relationship between systemic blood pressure and cerebrospinal fluid pressure. All cases in which extraneous factors might influence the cerebrospinal fluid pressure were therefore excluded. The cases excluded were those of: (1) tumor and abscess of the brain; (2) acute infections of the central nervous system, such as meningitis, poliomyelitis, encephalitis and syphilis of the central nervous system; (3) cerebral edemas associated with acute systemic infections and intoxications, such as acute febrile diseases, eclampsia, uremia and chronic and acute nephritis; (4) cerebral hemorrhages; (5) congestive heart failure (these cases were excluded because of the effect of the commonly associated disturbance of the venous pressure on the cere-

brospinal fluid pressure), and (6) epilepsy. Since there is some question as to the influence of epilepsy on intracranial pressure, all cases of convulsive seizure were eliminated.

For analysis, we divided the 1,418 cases into groups according to the systolic and diastolic blood pressure.

In table 1 the cases are divided into groups according to the level of the systolic blood pressure. In 970 cases with the systolic blood

TABLE 1.—*Summary of the Influence of Systolic Blood Pressure on Cerebrospinal Fluid Pressure*

Systolic Blood Pressure, Mm. of Mercury	Number of Cases	Average Cerebrospinal Fluid Pressure, Mm. of CSF*
Low (under 100 mm.)	70	120
Normal (100–150 mm.)	970	128
High (150–300 mm.)	378	143
Total	1,418	132

* CSF = cerebrospinal fluid.

TABLE 2.—*The Influence of Systolic Blood Pressure on Cerebrospinal Fluid Pressure*

Systolic Blood Pressure, Mm. of Mercury	Number of Cases	Average Cerebrospinal Fluid Pressure, Mm. of CSF*
Under 100	70	120
100-125	519	125
126-150	451	132
151-175	146	138
176-200	130	147
201-225	67	149
226-250	23	136
251-300	12	147
Total	1,418	132

* CSF = cerebrospinal fluid.

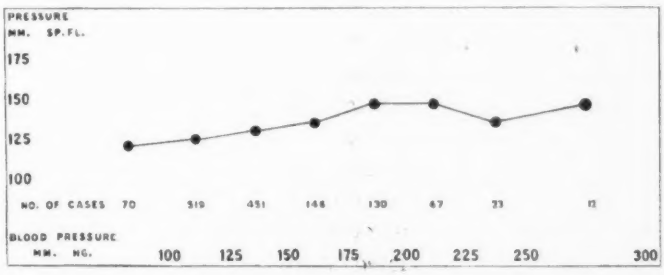

Chart 1.—Influence of systolic blood pressure on cerebrospinal fluid pressure (1,418 cases). This chart shows that in uncomplicated cases the average cerebrospinal fluid pressure is within normal limits regardless of the level of the systolic blood pressure and there is very little change in the cerebrospinal fluid pressure with a marked increase in systolic blood pressure.

pressure between 100 and 150 mm. of mercury, the cerebrospinal fluid pressure averaged 128 mm. of cerebrospinal fluid; in 70 cases with the systolic blood pressure under 100 mm., the cerebrospinal fluid pressure averaged 120 mm.; in 378 cases with the systolic blood pressure between 150 and 300 mm., the cerebrospinal fluid pressure averaged 143 mm. The average cerebrospinal fluid pressure for each group was, therefore, well within normal limits. There were 8 cases, however, in which the cerebrospinal fluid pressure was over 200 mm. These were scattered throughout the various groups. Most of them were, however, in the groups with high blood pressure. It is of interest to note that in the 19 cases with a systolic blood pressure of over 225 mm. of mercury, none had a cerebrospinal fluid pressure of over 200 mm. of cerebrospinal fluid. Thus an average increase of more than 100 mm. of mercury (1,360 mm. of water) in the systolic blood pressure was accompanied by an average increase of only 23 mm. of cerebrospinal fluid (1.4 mm. of mercury) in the cerebrospinal fluid pressure.

Table 2 shows the 1,418 cases divided into groups according to the systolic blood pressure. Chart 1 is a graphic representation. It is evident from these data that variations in the systolic blood pressure from less than 100 mm. to over 250 mm. of mercury have no significant influence on the cerebrospinal fluid pressure. With elevated blood pressure, the average cerebrospinal fluid pressure shows a slight tendency to be a few millimeters higher, but even with extremely elevated blood pressure the average cerebrospinal fluid pressure is well within normal limits, the total range for all of the groups being only from 120 to 149 mm. of cerebrospinal fluid.

Group II: Influence of Diastolic Blood Pressure on Cerebrospinal Fluid Pressure.—In table 3, the 1,418 cases are analyzed according to the level of the diastolic blood pressure. It is seen that in 72 cases with the diastolic blood pressure under 60 mm. of mercury, the cerebrospinal fluid pressure averaged 124 mm. of cerebrospinal fluid; in 1,051 cases with the diastolic blood pressure between 60 and 100 mm., the cerebrospinal fluid pressure averaged 130 mm.; in 295 cases with the diastolic blood pressure between 100 and 200 mm. of mercury, the cerebrospinal fluid pressure averaged 135 mm. of cerebrospinal fluid.

Thus an average increase of more than 80 mm. of mercury (1,088 mm. of water) in the diastolic blood pressure was accompanied by an average increase of only 11 mm. of cerebrospinal fluid (0.9 mm. of mercury) in the cerebrospinal fluid pressure.

In table 4 the cases are divided into groups according to 20 mm. of difference in the diastolic blood pressure. Chart 2 is a graphic representation.

TABLE 3.—*A Summary of the Influence of Diastolic Blood Pressure on Cerebrospinal Fluid Pressure*

Diastolic Blood Pressure, Mm. of Mercury	Number of Cases	Average Cerebrospinal Fluid Pressure, Mm. of CSF*
Low (under 60 mm.)	72	124
Normal (60-99 mm.)	1,051	130
High (100-200 mm.)	295	135
Total	1,418	132

* CSF = cerebrospinal fluid.

TABLE 4.—*The Influence of Diastolic Blood Pressure on Cerebrospinal Fluid Pressure*

Diastolic Blood Pressure, Mm. of Mercury	Number of Cases	Average Cerebrospinal Fluid Pressure, Mm. of CSF*
Under 40	6	98
40- 59	66	128
60- 79	505	126
80- 99	546	134
100-119	201	130
120-139	72	148
140-159	19	135
160-200	3	161
Total	1,418	132

* CSF = cerebrospinal fluid.

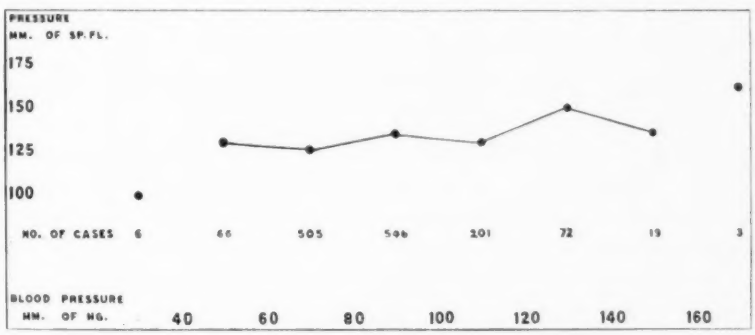

Chart 2.—Influence of diastolic blood pressure on cerebrospinal fluid pressure (1,418 cases). This chart shows that in uncomplicated cases the average cerebrospinal fluid pressure is within normal limits regardless of the diastolic blood pressure level and that there is very little change in the average cerebrospinal fluid pressure with a marked increase in the diastolic blood pressure. Only the 6 cases showing a diastolic blood pressure below 60 mm. and the 3 cases with a diastolic pressure above 160 mm. presented significant variations in the cerebrospinal fluid pressure.

Group III: Influence of Arterial Blood Pressure on Cerebrospinal Fluid Pressure in Patients with Uremia and Congestive Heart Failure.—In this group are included all cases in which the nonprotein nitrogen of the blood was greater than 100 mg. per hundred cubic centimeters, and all of the cases of congestive heart failure as evidenced by subcutaneous edema, fluid in the serous cavities or orthopnea.

Table 5 shows that in uremia and in congestive heart failure the average cerebrospinal fluid pressure was distinctly elevated, regardless of the arterial blood pressure. There was a tendency for the patients with the highest arterial pressure to have a higher average cerebrospinal fluid pressure. This may be explained on the basis that patients with the highest blood pressure are apt to be the most severely decompensated or to be suffering from a severer degree of uremia.

TABLE 5.—*The Influence of Systolic Blood Pressure on Cerebrospinal Fluid Pressure in Uremia and Congestive Heart Failure in Sixty-Six Cases*

Systolic Blood Pressure, Mm. of Mercury	Number of Cases	Average Cerebrospinal Fluid Pressure, Mm. of CSF*
100-125	11	249
126-150	9	265
151-175	10	215
176-200	9	255
201-225	13	286
226-300	14	313
Total	66	271

* CSF = cerebrospinal fluid.

Group IV: Influence of Cerebrospinal Fluid Pressure on Arterial Blood Pressure in Patients with Increased Intracranial Pressure.—This group is composed of 122 cases of tumor or abscess of the brain, meningitis and similar conditions in which there was an increase in the cerebrospinal fluid pressure.

Table 6 and chart 3 show the variation in systolic and diastolic blood pressure with the cerebrospinal fluid pressure varying between 200 and 800 mm. The average for the group was 122 systolic and 75 diastolic, and there was practically no variation in either the systolic or the diastolic arterial blood pressure in any of the groups except the group with a cerebrospinal fluid pressure between 600 and 700 mm. of cerebrospinal fluid, in which the average was 152 systolic and 85 diastolic. There were only 3 cases in this group.

Of the cases in which determinations of the cerebrospinal fluid and blood pressure were made simultaneously, there were only 2 in which the cerebrospinal fluid pressure was over 800 mm. In both of these cases the

cerebrospinal fluid pressure was over 1,000 mm., and the systolic and diastolic blood pressures were both markedly elevated, being over 200 and 100 mm. of mercury respectively.

TABLE 6.—*Influence of High Intracranial Pressure on Arterial Pressure in One Hundred and Twenty-Two Cases*

Cerebrospinal Fluid Pressure, Mm. of CSF*	Number of Cases	Average Blood Pressure, Mm. of Mercury	
		Systolic	Diastolic
200-299	41	121	75
300-399	40	121	75
400-499	19	116	74
500-599	14	126	74
600-699	3	152	85
700-799	5	127	79
Total	122	122	75

* CSF = cerebrospinal fluid.

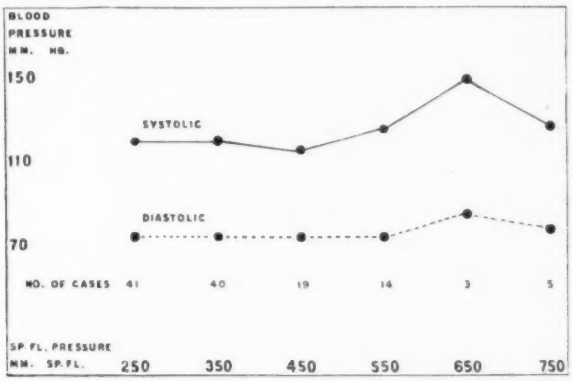

Chart 3.—Relationship of blood pressure to cerebrospinal fluid pressure in 122 cases showing a high intracranial pressure. This chart shows that there is practically no change in the systolic and diastolic blood pressures with the ranges of intracranial pressures usually encountered (from 200 to 800 mm. of cerebrospinal fluid).

COMMENT

It is evident from our data that there is no simple relationship between either systolic or diastolic blood pressure and cerebrospinal fluid pressure. This confirms the findings of Shelburne, Blain and O'Hare. In 1 patient they were able to raise the systolic blood pressure to 200 mg. of mercury by occlusion of a femoral arteriovenous aneurysm without any influence on the spinal fluid pressure.

Our data also clearly demonstrate that increases in cerebrospinal fluid pressure have no appreciable effect on either systolic or diastolic

blood pressure until the spinal fluid pressure reaches the level of the diastolic blood pressure. The theoretical considerations involved in the relationship between cerebrospinal fluid pressure and blood pressure and particularly the mechanism by which cerebral circulation is maintained in the face of a rising intracranial pressure have been detailed by Fremont-Smith and Kubie [1] and will not be repeated here. Shelburne, Blain and O'Hare [6] have called attention to a small group of cases of vascular hypertension in which an elevated cerebrospinal fluid pressure occurs which is apparently not due to cardiac or renal decompensation. Six of our 8 cases of unexplained high intracranial pressure showed high blood pressures and belonged to the same group described by Shelburne, Blain and O'Hare. These cases deserve further study.

SUMMARY

1. A comparison of the cerebrospinal fluid pressure and the arterial blood pressure is given for 1,418 cases in which all known extraneous factors that might influence cerebrospinal fluid pressure were eliminated. In this group the arterial blood varied from below 100 to 300 mm. systolic and from below 40 to 200 mm. diastolic. The average cerebrospinal fluid pressure was 132 mm., and the average in the patients with low systolic or diastolic blood pressure was not appreciably different from that in the patients with high systolic or diastolic blood pressure.

2. A comparison of the average cerebrospinal fluid pressure and the systolic blood pressure is given for 66 cases of uremia and congestive heart failure, and it is shown that the cerebrospinal fluid pressure was distinctly elevated in all groups, regardless of the blood pressure. There was a tendency for the cases with the highest blood pressure to have the highest cerebrospinal fluid pressure.

3. A comparison of the cerebrospinal fluid pressure and the systolic and diastolic blood pressures is given for 122 cases of a high intracranial pressure due to increased intracranial content. It is shown that there was no definite change in the blood pressure with an increase of less than 800 mm. in the cerebrospinal fluid pressure.

CONCLUSIONS

1. In uncomplicated cases there was no relationship between the cerebrospinal fluid pressure and the arterial blood pressure, either systolic or diastolic.

2. There was a definite increase in the cerebrospinal fluid pressure in cases of uremia and congestive heart failure.

3. An increase in the intracranial pressure had no effect on arterial pressure until the level of the cerebrospinal fluid pressure exceeded that of the diastolic pressure.

4. There were occasional uncomplicated cases of arterial hypertension (6 of our series of 1,418) in which the cerebrospinal fluid pressure was over 200 mm. of cerebrospinal fluid. We have no explanation for this.

DISCUSSION

Dr. Colin K. Russel, Montreal, Canada: From your experience can you tell whether a sudden increase in intracranial pressure such as occurs in a subarachnoid hemorrhage influences the blood pressure to any extent?

Dr. John Favill, Chicago: Is the proportion which the volume of cerebral blood bears to the total volume of blood known? I have in mind that slight changes in the volume of the cerebral blood might cause important functional disturbances without significant changes in the blood pressure.

Dr. H. Houston Merritt, Boston: It is my opinion that there is much more apt to be a change in the systemic arterial pressure if the increase in the cerebrospinal fluid pressure is sudden; that is, the level of the intracranial pressure will not have to be so high to influence systemic blood pressure if the increase is sudden. If the increase is gradual, a higher level will be reached before compensation takes place.

I have no data with regard to the effect of the volume of cerebral blood on the systemic blood pressure.

PSYCHOPATHOLOGY

A PLEA FOR A MORE CONSTRUCTIVE ATTITUDE

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I shall base my brief discussion on the case histories of three patients. The histories are redeemed only from the commonplace by a single merit. They are not unusual. They represent a large cross-section, not of the practice of psychiatry but of the practice of medicine. One is not obliged to look for them in the consulting rooms of the psychiatrist. With the proper mental perspective one may find them by the dozens in the offices of the general practitioner, the internist, the neurologist, the surgeon, the gastro-enterologist, the genito-urinary specialist, the gynecologist, the laryngologist and others who travel the highways and by-paths of the art of medicine. They teach two lessons. The first is a philosophic one—that appearances are often deceptive; the second is a practical one—that perhaps some revision is needed concerning the values that go into the making of a diagnosis and that subsequently dictate the treatment of the patient.

REPORTS OF CASES

CASE 1.—The patient, a man, aged 49, was married; his wife was aged 35, and there were two healthy normal children. At the first interview he was anxious to the point of desperation because, as he stated, for the past eighteen months he had been sexually impotent. Pathetic in his earnestness, he related the steps he had taken to regain potency and happiness; instrumentation by genito-urinary specialists, prostatic massage, general massage, hydrotherapy, electrotherapy and heliotherapy. Then followed a display of faithfully kept copies of prescriptions for endocrine products: thyroid, pituitary and testicular. The patient claimed that he was worse. Not only did he have the impotence, but a long train of symptoms: annoying pains and disturbing sensations in the perineum, burning on urination, nocturnal emissions, headache, loss of energy, insomnia, reduction of concentration. The symptoms he described may be found accurately recorded in any patent medicine almanac.

CASE 2.—A married woman, aged 42, described chiefly gastro-intestinal symptoms: nausea, vomiting, "sick stomach," anorexia, headache, backache, and dizziness. She came merely for a "friendly conversation" with the psychiatrist, having been urged to do so. She had had two rest cures, numerous gastro-intestinal x-ray studies, had worn special corsets for gastroptosis and was having weekly gall-bladder drainages.

Read at George Washington University, Nov. 19, 1932.

CASE 3.—A likeable man, aged 22, who was studying accounting and commerce, managed to get through the first year with great difficulty. In the second month of the second year, he was ready to "give up the ship" because, he stated, "I am too sick to go on, and, frankly, I should rather quit than flunk. It is no use trying, I cannot concentrate."

He had never been robust. Tuberculosis had been suspected. There was much nose and throat involvement and frequent treatments were needed to shrink down a periodically congested nasal mucosa. He was underweight, and many dietary and rest regimens had been instituted to bring about a gain.

COMMENT

In the barest outlines of surface symptomatology and therapy, I have presented three common clinical situations. Before stating what I consider as a somewhat deadly parallel of underlying emotional factors, I ask that the conclusions take into account these two premises: First, there is not any intention of implying that measures of physical diagnosis and treatment are not useful and important. The doctrine of keeping the body sound and of correcting promptly its defects and its pathologic processes is well established and needs no brief. Not only is a thorough physical examination a necessary part of every psychiatric study, but in some instances the uncovering of organic disease may be not only very helpful but even life-saving. There is a point, however, beyond which physical diagnostic efforts and therapy may become harmful and even pernicious. This is certainly so if they exclude a consideration of emotional factors; if they are intensively and solely directed at the correction of minor and conjectural physical defects, such as slight deviations of the nasal septum, on the assumption that a minor operation will cure a psychoneurosis, or finally, if they are mistakenly focused on the physical expression of underlying emotional states. A patient of mine with a severe anxiety neurosis was treated for many months for hyperthyroidism, seemingly because he had a rapid pulse, rather staring eyes and a few vasomotor disturbances.

The second premise is that the statement I am about to make concerning emotional factors in the patients under consideration is confined purposely to surface psychopathology. Whatever was discovered by a deeper penetration of the psyche of these patients is omitted. Nothing is presented that could not be found with somewhat less effort and with a smaller outlay of time than is needed to arrange for and interpret a gastro-intestinal roentgen study.

A brief review may now be made of certain emotional factors that were easily determined in the three patients.

Case 1.—The man with sexual impotence had been dominated far into manhood by an aggressive, positive mother. He was fourteen years older than his wife, whose sex needs were strong; his neurosis began soon after an unsuccessful attempt at sex relations a short time after

quite a successful relationship. He thought that his wife seemed irritated and impatient at the failure, because they had often had sex communion twice in a short space of time. The entire situation was so lightly repressed that it was revealed easily at the first interview.

Case 2.—The woman with the train of gastro-intestinal symptoms had little or no sex desire. Sex relations had become for her a painful, unpleasant affair. She concealed her revulsion more or less successfully but tried by various subterfuges to decrease the frequency of the sex act. For some time she had feared that her husband would tire of her and leave her. As a matter of fact, just before the onset of the neurosis her husband had accused her rather pointedly of sexual indifference.

Case 3.—The young student at the first interview readily and anxiously confessed to occasional masturbation. His relief at the opportunity to unburden his troubled and remorseful mind was enormous. It was fairly obvious that during most of his life he had been tied a bit too tightly to his mother's apron strings and had been excessively warned about "girls." The masturbation had not been continuous from childhood, but had been taken up rather recently following three heterosexual experiences which unfortunately occurred in a setting conducive to fear, embarrassment and feelings of inferiority.

Perhaps it may be thought that there is not much choice between the physical and emotional pictures that I have rather crudely sketched. On the one hand there were the various genito-urinary examinations, gastro-intestinal and gallbladder tests, studies of the nose, throat and sinuses and x-ray pictures of the chest; on the other, a revealing of three emotional conflicts. The first, the physical, dictated a variety of physical therapy, urethral instrumentation, prostatic massage, general massage, hydrotherapy, electrotherapy, heliotherapy, endocrine medication, the wearing of special corsets, gallbladder drainage, treatment of the nose and throat, rest and diets; the second, the emotional, led to a moderate amount of psychotherapy, to the opportunity to talk over troubles that were not physical, to explanation of underlying mechanisms and a frank facing of their implications, to correction of faulty mental attitudes, and to slight adjustments in the environment.

Danger Arising From the Neglect of a Consideration of Psychopathologic Mechanisms.—From time to time psychiatrists have been warned, and probably rightly warned, of the danger of neglecting possible physical factors. They have made mistakes in this direction, and I believe that they have profited by them. Their mistakes in this direction stand out like sore thumbs. If a psychiatrist fails to recognize a tumor of the brain, his error will stand out as an accusation against him until the end of time. Psychiatrists now think that they have a page of experience to present that deserves reading. They are inclined

to insist that, injudiciously applied, the more purely physical, diagnostic and therapeutic measures may do as much harm as they do good if wisely utilized. Indeed, it is known by psychiatrists that, used unwisely, these measures may make and fix a neurosis rather than cure it. I think that practically all modern psychiatrists, conscious of the help they have so generously received from fellow practitioners and without the least intention of decrying wise diagnostic and therapeutic procedures, would nevertheless ask that certain elementary considerations in psychopathology be added to the armamentarium of every practitioner of medicine. They would ask that these considerations be received not as abstract armchair psychology but as real dynamic facts and as factors every whit as actual and important as catarrhal inflammations of the nasal membrane, ptosis of the stomach, bronchial thickening of the chest, muscle imbalance of the eye or endocrine dyscrasias and, sometimes (this I say with my tongue in my cheek), as important as the demonstration of the bacillus of Koch in the sputum.

Elementary Considerations in Psychopathology.—A statement has been made, and there must be no hesitancy in putting forth at least a few of the psychopathologic mechanisms which psychiatrists believe to be operative, and which may and frequently do become disguised as deceptive physical symptoms and even signs.

First, let me make a simple comparison that is more or less valid. Frequently, a practitioner has the experience of observing on the surface a striking symptom, the real reason for which is somewhat hidden and is only accessible to careful investigation, as, for example, the eyeground picture in certain severe varieties of renal intoxication or in tumor of the brain. Thus, also, the reason for many clinical manifestations that seem to be organic and often present definite physical symptoms is not obvious at once to conscious scrutiny. This has been proved so often that it would be pointless to discuss it again. Therefore, if there were no other proofs (but there are many) this alone would be sufficient to ask for belief in the existence of a mind, the content of which is not apparent or evident on the surface, or, I may say, is not made conscious to the individual or to the observer. Whether this mind is called subconscious or unconscious is not of great moment in this informal presentation. Neither does it matter greatly whether one accepts as a minimum evaluation of the content of this nonconscious mind that it contains in some shape or form traces of everything that has happened to the person during the previous years of his life, or as a maximum evaluation that it is a repository of much more than that, extending back, for instance, into the dim evolutionary history of the human species. After all, the important thing is the acceptance by the practitioner of the fact that there is such a mind, and that probably at least one-half the symptoms he sees in his patients have a

subconscious or unconscious origin. If this is true, then there is here a dynamic conception and one should be just as industrious in ferreting out concealed unconscious pathology as in searching for deep-seated organic disease that is far removed from the surface complaint for which the patient seeks relief.

Physicians who regard the bodies of their patients scientifically begin to see things more or less clearly before they have actually happened. If questioned, the physician could not demonstrate these potentials with any exactitude, but he would probably speak of them as tendencies—tendencies to develop heart disease, arteriosclerosis, gallbladder disease, etc. This question of physical habitus or potentials is at the present time stimulating the writing of one of the most brilliant chapters in the art of medicine. Whatever these potentials may be, it is clear that they indicate lessened resistance in certain directions and are possibly sources of danger. So, too, in the hidden mental life of people various trends are formed according to past experiences, and some of these constitute potential sources of danger. For want of a better term one thinks of mental "complexes" instead of innate physical tendencies. A complex may be traditionally defined as a group of ideas held together by a strong emotional bond and demanding expression in consciousness. Frequently, perhaps usually, complexes are expressed in the conscious everyday life as harmless activities, such as collecting stamps or coins, or even as constructive energies that we devote, for instance, to various philanthropic movements or to worth-while occupational endeavors. There are two conditions at least under which the complex may be harmful. The first of these conditions is that the complex falls too far short of the ego of the person, which in a few words is his measuring rod, a kind of self-criterion of what he should be, the self-ideal. The second condition is that the complex is of such a nature that if it should attempt to express itself directly in action it would at once encounter the censure of society, the adverse judgment of the herd—as, for instance, a homosexual complex. The complex being denied expression in everyday conscious life, the way is naturally paved for the conflict.

If one is able to accept the actuality of the complex as being at least as real as certain somatic tendencies, then of necessity one must subscribe to the reality of the conflict that ensues when complexes run counter to the self-ideal or to the current social code. Conflict, of course, means struggle. Mental conflict, therefore, refers to the struggle or clash between the various and often sharply divergent tendencies of the mind. Desires and tendencies are almost without number, but they fall into three great categories, the ego, the sex and the herd desires, and it does not seem too much to say that at the roots of many clinical physical symptoms there is the warring between the often

irreconcilable demands of self, of sex and of society. But these considerations again must go beyond mere interesting speculation. If they are to have clinical and therapeutic application, they must be clearly apprehended. The psychiatrist would be inclined to say that the clinician dare not fail to take cognizance of them. After all there is a choice. If, as in a patient I saw recently, vomiting of such force and character that it led to numerous examinations for tumor of the brain can be due to a conflict between love for a mistress and duty toward wife and children; if symptoms mistaken for hyperthyroidism in a young broker can be occasioned by the protest of his ego against rather questionable business methods practiced by his firm; if, as in the three patients whose records I have cited, a train of genito-urinary symptoms may be referred to the patient's fear of being unable to meet the sex needs of his wife, a group of gastro-intestinal disturbances are caused by an inability to reconcile psychologic sex capacity and the desire to retain the regard and protection of the husband or as in the third instance, a clash between mother fixation and the self and herd expectation of heterosexual love leads to such poor health that it is thought to be tuberculosis; and if, finally, it is remembered that these are but a few of the hundreds of situations seen daily by clinicians in which mental conflicts have been converted into physical symptoms, it should be apparent that some appreciation of at least the elements of psychopathology is constantly needed, and that when physical therapy, no matter how skilfully applied, is directed at symptoms with a basis in the mental life of the patient, the result is sure to be disappointing. Indeed one may even go a bit further and say that under such conditions physical therapy not only will be disappointing but will be distinctly harmful to the patient. It provides a definite path of escape from the painful recognition of psychogenic difficulties, and the further the patient is led along this path, the further is he being taken away from the possibility of self-knowledge and adjustment.

A thoughtful internist must frequently reflect on the very great variety and complexity of changes that occur in the physical bodies of his patients in the courses of their lives. Likewise must he speculate on the reasons for such changes. In a broad sense, I presume he feels that, beginning with certain potentials hereditarily determined, there follow a shaping and a molding according to the conditions of life. In any event, physical surface alterations and phenomena are in a sense a response to somatic inclinations that have in some fashion or another become a significant factor in the body of a particular person. It is not stretching the comparison too far to say that from time to time there result from the contact with the environment certain happenings that definitely influence the future physical history of the subject. For instance, obesity determined by conditions of living may result in a dangerous limitation of exercise, and in the next analysis

there may be significant and detrimental changes produced in the entire organic life and structure of the patient. As there is a stream of somatic life, so is there a stream of mental life. Starting in a certain direction, unquestionably the flow is influenced by all the emotional experiences, many of them not at all apparent on the surface. It is particularly those experiences *not apparent on the surface* that are strongly dynamic in shaping the psyche, and likewise they are the origin of the psychopathology which later will come to the surface in puzzling and deceptive forms. Much of the concealed material is accumulated by a process of repression, and repression may be considered as "purposeful forgetting," that is, as a submerging of thoughts to which strong and unpleasant feelings are attached and the implications of which would be extremely difficult to face openly and consciously. Repression is not equivalent to effacement; that fact must be stressed here precisely because many of the symptoms presenting as physical phenomena to the physicians are undoubtedly the distorted peripheral expression of repressed emotional material.

GENERAL COMMENT

Perhaps I have pursued the comparison of the physical and the psychic too far. It is understood, of course, that physical and psychic are so interrelated that they are not to be separated, but for the purpose of easier understanding it is useful to make the comparison. One may then think of physical symptoms not only as having a hidden origin in the previous physical experiences of the patient, but also frequently as having a concealed starting point in his former emotional experiences. If a psychiatrist should go to an internist and in good faith ask "What is the most important thing you can tell me that will help me in my work?" the answer might well be, "Be careful that you do not mistake the organic for the functional. If you do, you might erroneously continue to treat organic disease by psychotherapy until it is too late, and the patient has lost his chance for recovery." If the internist should come to the psychiatrist and ask, "What can you tell me from your psychiatric experience that will help me in the understanding and treatment of my patients?" the answer would be about as follows: "Be ever on your guard that you are not misled into treating functional symptoms as organic and thus, perhaps, fixing for all time crippling psychic invalidism in your patients. If after reasonable study and investigation you cannot find at least fairly definite somatic disease, do not without further thought enter the highly theoretical field of questionable and conjectural therapy involved in endless treatments directed at very minor defects. If the cause of the symptoms is an unsolved emotional problem (and I am tempted to add, even if it is not) nothing but a deeper, firmer rooting of symptoms can result

from such measures as operations for fractional deviations of the nasal septum, cumbersome apparatus or even surgical operations for slight degrees of ptosis of the stomach, endless refractions for somewhat hypothetical imbalances of the ocular muscles, gastric lavage and gallbladder drainage for conditions of the stomach and gallbladder that cannot be substantiated by the usual tests, highly artificialized diets and many other things." The psychiatrist would warn the internist to refrain from entering these therapeutic pathways that so often have a blind end until at least some explorations have been made for factors in the emotional life. Probably, too, the psychiatrist would recall large groups of anxiety states in which a puzzling assortment of vasomotor phenomena simulated organic disease. If they are dealt with solely on an endocrine basis without reference to underlying unsolved conflicts and their resultant emotional reactions, the outcome will not be satisfactory. If, finally, the internist asked for the very minimum of a body of knowledge that would permit the treatment of patients whose symptoms are emotionally and not organically determined, or at least enable him to suspect such situations, the reply would be that the very smallest amount of information must at least embrace the following: First, there is a mind whose content is concealed and is not within the horizon of the everyday conscious scrutiny of the patient or of his doctor. Second, the stream of this nonconscious life is significant in determining conscious behavior, and it often contains material or complexes frequently representing the repressed memory of previous highly charged emotional experiences that not only have a driving force but cannot be reconciled to the ego of the individual and the demands of the social code. Third, when a compromise cannot be effected, the conflict ensues, and this may readily be converted into misleading physical symptoms. It is highly advisable for the clinician to subject every symptom or sign for which he cannot find a satisfactory somatic explanation to the criterion of these few and elementary considerations of psychopathology.

I am afraid I have suggested that the physical symptoms presented by a given patient must all be either organic or functional in origin. This is not true. Frequently they are both. I presume that for every patient whose symptomatology is readily understandable to the clinician there are at least five in whom the symptoms are not at all clearcut. Sometimes the symptoms that are confusing run hand in hand with those that are readily explainable on the basis of organic disease; often after the resolution of organic disease certain symptoms difficult to explain persistently remain. This is a rather large segment of the practice of medicine. In the wake of any illness, after any surgical operation—even minor ones like tonsillectomy or the extraction of a tooth—after normal childbirth, after trauma and in the diseases of

childhood, symptoms frequently arise that cannot be referred to the original disturbance except by a display of mental gymnastics on the part of the clinician that is more interesting than scientifically valid. The reason is obvious. In the majority of cases these symptoms are not organic but functional; that is, they are not somatically but emotionally determined. The frequency of such situations is not at all surprising. The psyche of every human being is to some extent, at least, a battleground of conflicting trends, desires and emotions. The majority of us, nevertheless, "carry on" satisfactorily enough by a series of more or less adequate compromises. Let there occur, however, a flaw in the armor presented to the environment, perhaps by reason of a physical incapacity, and there are at hand the opportunity and the psychologic temptation to ease the conflict by employing the mechanism that converts emotional problems into physical symptoms. The clinical therapeutic moral is obvious.

I have discussed in an incomplete manner the very modicum of psychopathology that should be the daily stock-in-trade of the clinician in every branch of medicine, and I have confined myself to a consideration of those psychopathologic mechanisms that are chiefly concerned with emotional difficulties presenting themselves in the guise of physical symptoms. Naturally, there are many other mechanisms. They are less directly operative in the formula that begins emotionally and ends as a physical expression, but at least they should be mentioned. There is overcompensation, which is an effort, often expressed in the shape of extremely puzzling behavior, to keep something out of consciousness. There is rationalization, a psychopathologic device that keeps us from seeing ourselves as others see us. There is segregation, a stratagem by which emotional material is segregated or kept in a separate channel so that the conduct that flows from it is quite inconsistent with the remainder of the behavior. There are displacement, substitution and symbolism in which disagreeable and painful experiences are displaced from consciousness and reappear in the guise of seemingly harmless substitutes that are symbolic. There is projection, a method of escaping self-blame by shifting the blame to others or to the conditions of life. There is identification, a method too of escaping self-blame by submerging personal weaknesses and defects in the psychologic identification of ourselves with others who possess the ideals that we admire and desire. And there are many other considerations that are potent, like strong feelings of inferiority that perhaps may lead to such frantic and unwise efforts at compensation that a neurosis or even a psychosis is the only solution. It is true that these matters are not of primary importance for the clinician, but they do have some bearing on his problems. There is something that for want of a better word may be called morale. These psychopathologic mecha-

nisms, at least in their marked degrees, lessen morale, and, conceivably, the recuperative forces of the body are weakened if the emotional morale is at low ebb.

SUMMARY

The discussion of the subjects that have been presented in this paper may easily lead into devious channels; therefore, the agenda of what has been said may be stated as follows:

1. In the reports of three cases the attempt was made to present the surface physical symptomatology, the supposed organic bases and the resultant physical therapy, and to contrast these with the real underlying emotional factors and the psychotherapy that came from appreciating and understanding them.

2. The cases discussed were not unusual and represent a large cross-section of the general practice of medicine and its specialities. If certain elements of psychopathology are not appreciated, it would seem obvious that surface physical symptoms arising from an emotional basis will be treated purely along the lines of physical therapy. Such therapy in these instances not only is unscientific but is apt to harm the patient by fixing the symptoms.

3. In its most meager outlines the body of knowledge concerning psychopathology that the practitioner should accept and utilize in his daily clinical work must include some understanding of a nonconscious mind containing material which, though it is not within the scope of awareness, is nevertheless extremely potent in determining behavior. Much of this material has entered the nonconscious mind by a process of the repression of highly charged emotional experiences. When, as often happens, there is a conflict between conscious and nonconscious tendencies and desires, the conflict may be and often is manifested as physical symptoms. The connection and dependence of these symptoms with and on the underlying emotional basis is often as clear and reliable as the dependence of the cough, fever and loss of weight of tuberculosis on the bacillus of Koch in the body of the patient, or the convulsions of dementia paralytica on the effect produced by the presence of the spirochete.

4. These considerations are as important in partial as they are in total situations. If they are considered, it is likely that a fairly large percentage of puzzling symptoms complicating an organic clinical picture will be explained and that by their relief recovery may be hastened.

5. There is a fairly large body of rather well substantiated psychopathologic knowledge which, though it may not be directly involved in the conversion of emotional problems into physical problems, should nevertheless be of interest to the practitioner, since it concerns situations that lower the morale of the patient and in a given case may interfere with the accomplishment of recovery within a reasonable time.

REFLEXES FROM THE KNEE JOINT

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Many well recognized reflexes are known to be induced by the stretching of muscles, but reflexes caused by movement of the joints have received little attention and, indeed, their existence is sometimes doubted. Goldscheider [1] experimented on sensations evoked by the passive movement of joints and showed that these were greatly influenced by the speed of movement of the joint. Sherrington [2] studied the crossed reflex known as Philippson's reflex, in which passive flexion of one leg caused extension of the opposite leg and foot. He also determined the cause of this reflex and stated:

> The observations, therefore, while they allow the supposition that the crossed reflex may, when the nerves of the joint are intact, be excited partly through articular receptors, show that the chief and essential seat of initiation of the reflex lies, not in the joint, but in the vastocrureus muscle.

It seemed worth while to search for the effects of movements of the joints themselves, independent of muscle stretch, particularly since McCouch and Alpers [3] have reported the presence in the knee joint of a reflex factor from the bursae. The experiments reported in this paper are concerned with the reflex responses of the vastus externus muscle of the decerebrate cat with passive movement of the knee joint.

METHOD

The muscles of the thigh and leg of a decerebrate cat were denervated or resected at their origins or insertions, with the exception of the vastocrureus muscle, which was resected just proximal to the patella in order to have the knee joint intact. The branches of the obturator and the internal saphenous and popliteal nerves which innervate the knee joint and articular capsule were left intact. The muscle used for recording was the vastus externus which was attached directly to the myograph. Care was taken to free the muscle from all surrounding tissues; the knee joint was likewise freed but not opened. The femur was firmly fixed with one drill through the great trochanter and another through the

From the Department of Physiology, University of Pennsylvania.

1. Goldscheider, Alfred: Arch. f. Physiol. 1889, p. 369.
2. Sherrington, C. S.: Quart. J. Exper. Physiol. **2**:109, 1909.
3. McCouch, G. P., and Alpers, B. J.: Arch. Neurol. & Psychiat. **22**:672 (Oct.) 1929.

epicondyles. The myograph used was a frictionless shadowgraph lever with the torsion wire fixed at both ends. The degree of shortening allowed for the tension developed was 0.75 mm. per hundred grams of tension. A rough estimate of the movements of the joint was obtained simultaneously by attaching the leg to an isotonic lever, the upward excursion of which denoted extension, while the downward denoted flexion of the knee joint. Though the system did not give a record of the quantitative movement, because of the fact that the needle shadow was linear while the leg motion was through an arc, the qualitative results may be taken as an indication of the presence or absence of leg movement and its direction, and may be interpreted accordingly.

With this arrangement, the muscle recorded could not be directly affected by passive flexion or extension of the knee joint accomplished by hand manipulation of the lower part of the leg, all structures below the knee having been previously denervated.

The recording was done at first on a fast kymograph, but later optical records were considered better as illustrative material and are consequently used in the following descriptions.

The effects of flexion or extension of the knee were tested and compared with those after anesthetization with a 4 per cent solution of procaine hydrochloride injected directly into the joint.

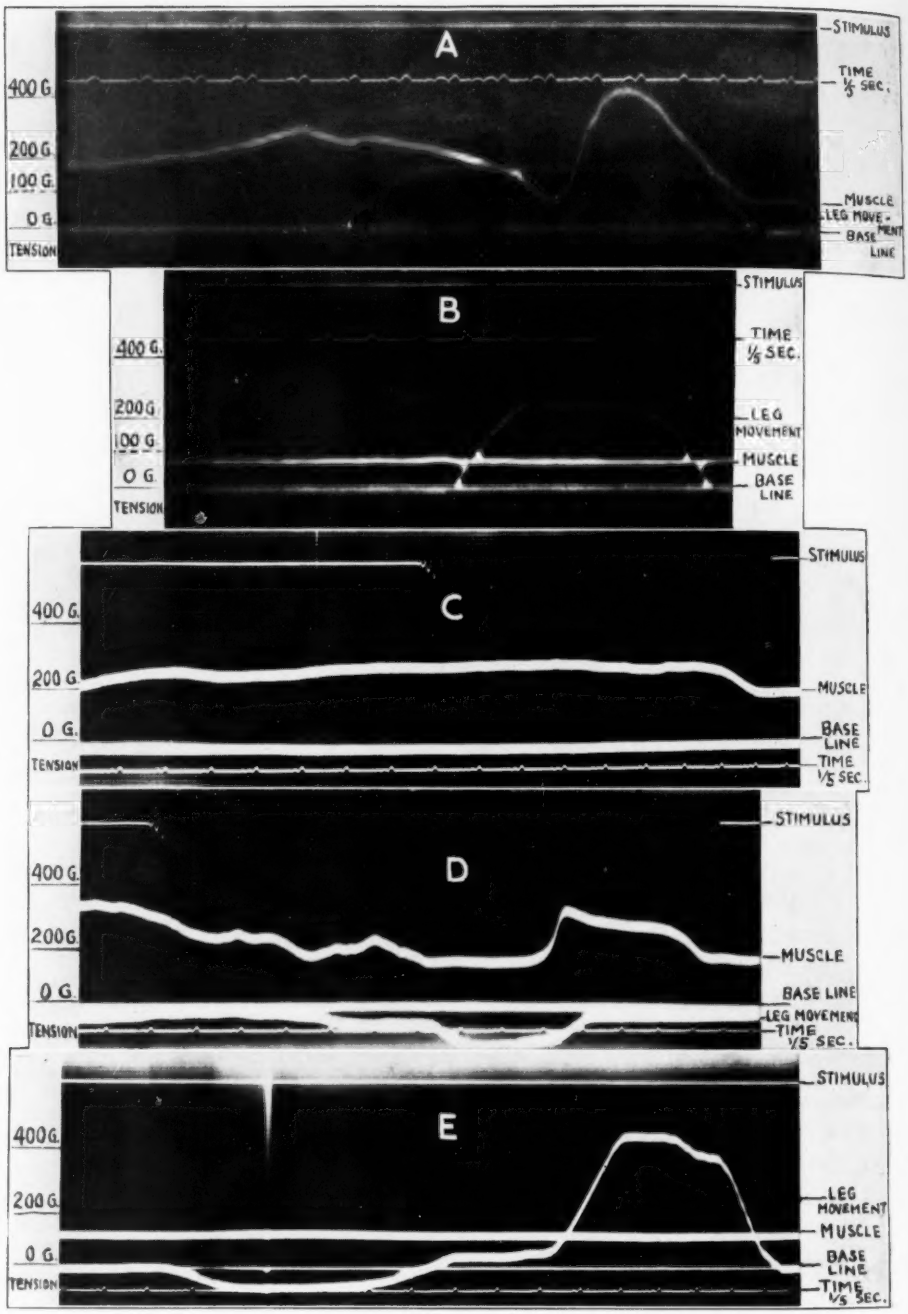
RESULTS

Nine experiments were performed, five with a kymograph, and four with optical records. Cocainization of the knee joint was attempted seven times, and satisfactory control records were obtained on all but one occasion. This experiment has been discarded.

Rapid passive extension induces a contraction which recruits rapidly to a tension of about 400 gm. and abruptly declines as the knee attains the completely extended posture, to recruit once more during the successive flexion, and relax only after considerable after-discharge as shown in the figure (*A*). The response to passive flexion is indistinguishable from that of passive extension. Both are abolished by a 4 per cent solution of procaine hydrochloride injected into the joint (*B*).

The relaxation on extreme extended or flexed posture might be due either to cessation of stimulation or to inhibition. This question was tested by repeating the movement of the joint on a background of contraction from stimulation of the contralateral sciatic nerve. *C* shows a control crossed reflex, and *D*, the response to knee flexion on this background. The contraction seen in *A* is here largely occluded. On attaining extreme flexion of the joint, however, there is abrupt inhibition of both the contraction from joint movement and that from stimulation of the contralateral sciatic nerve. *E* illustrates the absence of either contraction or artefact on extreme extension and flexion of the knee after cocainization.

It should be noted that in one experiment, in which the results were entirely negative from every point of view, no branch of the popliteal nerve to the knee, found in every other case, could be seen.



Read the records from right to left, and the movement of the leg as: extension, up; flexion, down. The time is one-fifth of a second. *A*, the effect of passive extension of the knee joint on the tension of the vastus externus. *B*, same as *A*, but after injection of 4 per cent procaine hydrochloride into the joint. *C*, crossed extension reflex by tetanic stimulation of the contralateral sciatic nerve at induction coil distance of 19 cm. *D*, the effect of flexion of the knee joint on a crossed extension reflex of the same strength as in *C*. *E*, absence of effect of passive extension and passive flexion after an injection of 4 per cent procaine hydrochloride into the joint.

COMMENT

The results suggest the presence of two sets of receptors in the knee: first, those that respond to the movement of the joint and produce, reflexly, contraction of the vastus externus; second, those that are stimulated by extreme positions and respond by reflex inhibition of the vastus externus.

Finally, there arises the question of the purpose of this twofold reflex response. As yet, this is uncertain, but the experiments performed raise the query whether or not the value of the increased tension may not be the fixation of the joint by extensor-flexor co-contraction. Adequate records of a flexor muscle must be made before this can be settled. The extensor inhibition at extreme joint posture may well be a reaction of liberation from an insupportable state, possibly to escape pain produced by this posture.

CONCLUSIONS

In the decerebrate cat with the knee joint and its innervation intact, passive flexion or extension of the knee induces contraction of the vastus externus followed, on attaining extreme flexed or extended posture, by inhibition.

SPECIAL ARTICLES

PRIMARY PARALYSIS AGITANS (PRIMARY ATROPHY OF EFFERENT STRIATAL AND PALLIDAL SYSTEMS)

FURTHER CONSIDERATION OF A SYSTEM DISEASE OF THE PARALYSIS AGITANS TYPE; ITS RELATION TO THE SYNDROMES OF THE CORPUS STRIATUM

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In May, 1916, at a meeting of the American Neurological Association, I [1] described a system disease of the paralysis agitans type associated with atrophy of the large efferent projection cells of the corpus striatum. The atrophic changes involved the cells of the globus pallidus the nucleus basalis and the large cells of the caudate nucleus and putamen. These I regarded as anatomically and physiologically related, constituting the efferent system of the corpus striatum, the globus pallidus mechanism. I called the condition progressive atrophy of the globus pallidus (primary atrophy of the efferent pallidal system).

One year later, I described [2] similar atrophic changes in the large efferent cells of the striatum in the presenile form of paralysis agitans.

The existence of a primary system disease in this region with selective involvement of nerve cells was a unique opportunity for an interpretation of the functions and symptomatology of the corpus striatum. As a result of these investigations, I took a definite position, both as to the nature and localization of paralysis agitans and as to the functions of the corpus striatum.

The corpus striatum was regarded as the great infracortical center for the control of paleokinetic or extrapyramidal function, exercising control over the automatic-associated types of movement. The large

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1. Hunt, J. R.: Progressive Atrophy of the Globus Pallidus (Primary Atrophy of the Pallidal System): A Contribution to the Functions of the Corpus Striatum, Brain **40**:58, 1917.

2. Hunt, J. R.: Primary Atrophy of the Pallidal System of the Corpus Striatum: A Contribution to the Nature and Pathology of Paralysis Agitans, Arch. Int. Med. **22**:647 (Nov.) 1918.

efferent projection cells of the neostriatum (neopallidal cells) together with the efferent neurons of the paleostriatum (pallidal cells) comprised the "efferent pallidal system of the corpus striatum." [3] As both types of cells, neostriatal and paleostriatal, were efferent and of the golgi type I, and as both were involved in the atrophic process, the view was expressed that they were all motor cells of the pallidal type and participated in the formation of the efferent pallidal system.

This efferent pallidal system I regarded as the essential motor system of this region comparable with the corticospinal system in the sphere of neokinetic or pyramidal tract motility. A primary lesion of this system or its secondary involvement would cause the syndrome of paralysis agitans, which I considered to be an essential type of central palsy of extrapyramidal origin, corresponding to the spastic paralysis of disease of the pyramidal tract.

Since that time there have appeared many contributions dealing with these problems, among which the comprehensive investigations of C. and O. Vogt,[4] published in 1920, and the thorough monographic studies of Jakob [5] and Lewy [6] in 1923 are especially deserving of mention. These writers, and others who have followed, have approached the problem largely from the standpoint of regional localization.

My object in reviewing this question is to emphasize again the importance of system-lesions of the corpus striatum in the light of the many advances which have been made in this field in recent years. In my earlier publications I used the nomenclature in vogue at that time. The caudate nucleus and the putamen were the neostriatum; the globus pallidus was the paleostriatum.

In the present paper I shall use the terms striatum and pallidum, as suggested by C. and O. Vogt, interchangeably with neostriatum and paleostriatum (globus pallidus).

PRIMARY PARALYSIS AGITANS (JUVENILE TYPE) (PRIMARY ATROPHY OF THE EFFERENT STRIATAL AND PALLIDAL SYSTEMS)

The case on which my conclusions were based was one presenting the clinical picture of juvenile paralysis agitans. In early childhood the patient had shown some slight evidences of facial immobility and awkwardness of movement before

3. Hunt, J. R.: The Efferent Pallidal System of the Corpus Striatum: A Consideration of Its Function and Symptomatology, J. Nerv. & Ment. Dis. **46**:211, 1917.

4. Vogt, Cécile, and O.: Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:631, 1920.

5. Jakob: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923, p. 99.

6. Lewy, F. H.: Tonus und Bewegung; Systematische Untersuchungen zur Pathologie und Pathogenese der Paralysis agitans, Berlin, Julius Springer, 1923, p. 171.

the appearance of a tremor of the left foot, which began at 15. This gradually extended to the left arm and was followed by progressive weakness and rigidity. One year later there was similar involvement of the opposite side, with typical parkinsonian attitude, facial expression and gait. At 20 there were dysarthria and tremor of the face, tongue and eyes. There was slow steady progression of the disease, terminating in complete rigidity with anarthria. Death occurred at 40 from exhaustion. In the earlier years the tremor was coarse and at times violent under the stress of emotion or attempted movement, and was almost universal. Although coarse, it was not of the intention type; it gradually diminished, as rigidity supervened.

The essential pathologic changes were confined to the corpus striatum. The cells of the globus pallidus were greatly reduced in number. Comparative cell counts showed this reduction to vary from one sixth to one half of the normal. The greater number of the remaining cells were in various stages of chronic atrophy. These cellular changes were not confined to the cells of the globus pallidus proper but were also evident in the nucleus basalis of Meynert, which lies beneath the globus pallidus and is phylogenetically closely related to the paleostriatum. The large cells of the caudate and putamen were also much reduced in number and in various stages of chronic atrophy. The cells of the substantia nigra and corpus luysi were normal.

Corresponding to the atrophy of the efferent cells of the corpus striatum, there was moderate thinning of the ansa lenticularis and peduncularis, the lenticular bundle of Forel, H2 and the strioluysian fibers. The capsule of the corpus luysi was less voluminous than usual, and the intraganglionic network was somewhat reduced. No other significant vascular, inflammatory or degenerative changes were noted.

This condition I regarded as a primary system disease, a selective degeneration or abiotrophy of the efferent projection systems of the corpus striatum.

The liver was somewhat diminished in size and congested, presenting a distinctly nutmeg-like appearance. There were no undulations on the surface or evidences of cirrhotic changes on the surface of section.[7]

In 1930, van Bogaert [8] described a similar case of primary juvenile paralysis agitans in which my pathologic observations and interpretations were essentially confirmed. Previous to this no case similar to my own had been recorded. Such cases when they do arise are of capital importance, as the selective nature of the lesion is such as to permit of a much more exact dissociation of function than when the

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7. Hall, in a monographic study of hepatolenticular degeneration (La dégénérescence hépato-lenticulaire, Paris, Masson et Cie, 1921, p. 279), raised the question of the hepatic changes in this case for which there was no justification. The histologic changes were those characteristic of the cyanotic or nutmeg-like liver and were in no sense related to the cirrhosis of Wilson's disease.

8. van Bogaert, L. M.: Contribution clinique et anatomique à l'étude de la paralysie agitante, juvénile primitive. Atrophie progressive du globe pâle de Ramsay Hunt, Rev. neurol. **2**:315, 1930.

striatum or pallidum is involved by focal or diffuse lesions in a purely regional sense.

In van Bogaert's case the disease appeared at the age of 7 years with tremor of the left arm, extending a few months later to the left leg. At 12 tremor appeared on the right side, later extending to the right leg. At 20 the tremor involved the inframaxillary region and there was increasing dysarthria. The tremor was marked, and the whole body shook. It was variable, sometimes appearing during intentional movements and also when the patient was at rest in the recumbent posture. The attitude was parkinsonian; there was anteropulsion and retropulsion; gestures were slow and impoverished, and rigidity was present in the thighs.

Pathologically, there was a diminution in number and degeneration of the large polygonal cells of the caudate nucleus and putamen. These changes were even more marked in the cells of the globus pallidus. Pigmentary degeneration was noted in a certain number of cells of the corpus luysi, of which the medullary network was normal. In the locus niger there was a slight reduction in number with some atrophy of the cells. The changes were slight and occurred only in single cells and were not of the intensity described in encephalitis or Parkinson's disease. The medullary network of the substantia nigra was preserved. The liver was normal.

Van Bogaert emphasized the marked involvement of the cells of the globus pallidus, the lesser degree of involvement of the large cells of the putamen and caudate nucleus and the slight changes in the corpus subthalamicum and locus niger. He regarded the condition as an essential abiotrophy of pallidal cells, which is susceptible of extension to associated physiologic systems.

So far as I am aware, no other histologic studies of this rare disease are on record. The limitation of the atrophic lesions to the cells of the efferent systems of the corpus striatum (striatal and pallidal) are characteristic of the malady. The changes noted in the corpus subthalamicum and locus niger were slight and are not uncommonly encountered with other lesions of the striopallidum. How important they are it is difficult to say. These infrapallidal systems are physiologically related, and such changes may represent a beginning abiotrophy in subjacent but related systems or they may be merely secondary in nature. These are questions for the future.

Clinically, the disease is characterized by the early age of onset, the gradual progress over a long period of years and the generalized tremor and rigidity of the paralysis agitans type.

Encephalitic parkinsonism may be ruled out by the absence of infection, the gradual progression and the nature of the pathologic changes. The exclusion of pseudosclerosis may present greater difficulties, but the well known criteria of this disease should be sufficient to cause its recognition.

Progressive pallidal degeneration, a familial disorder described by Winkelmann,[9] should also be considered in differential diagnosis. This disease also occurs in early life and is characterized by a progressive rigidity of extrapyramidal type unaccompanied by involuntary movements of any kind. In this disease there is extensive degeneration of the cells of the globus pallidus and the pars reticularis of the locus niger with dysmyelinization of the entire pallidum (status dysmyelinatus). The neostriatum in both cell and myelin structure is normal.

Hallervorden and Spatz[10] described a similar familial disease in which the lesions are not so strictly limited to the pallidum and in which involuntary movements are observed referable to associated lesions of the striatum.

PRIMARY PARALYSIS AGITANS (PRESENILE TYPE)

In May, 1917, at a meeting of the Association of American Physicians, I described[2] two cases of presenile paralysis agitans with characteristic atrophy of the large efferent cells of the neostriatum. This selective involvement of the giant cells of the striatum was regarded as evidence of the existence of a system localization occurring in paralysis agitans of later life. This type of the disease I regarded as primary in contradistinction to those of secondary origin, following vascular, inflammatory, toxic and neoplastic lesions.

A résumé of the findings follows:

CASE 1.—A man, aged 57, had presented typical symptoms of paralysis agitans for seven years. There were: general weakness and rigidity, with rhythmic tremors of the extremities, face and tongue, the parkinsonian mask, and the posture, attitude and gait characteristic of this disease. Death occurred from bronchopneumonia.

Histologic study revealed well marked atrophic changes in the large efferent cells of the striatum and the giant cells of the caudate nucleus and putamen.

The small ganglion cells of the caudate and putamen were well preserved. The cells of the globus pallidus were reduced in size and of a rounded and angular appearance. The blood vessels of the striatum and pallidum showed moderate arteriosclerotic changes with no areas of softening or hemorrhage; many perivascular spaces contained clumps of dark granular and yellowish pigment; the dilatation of the spaces in the more anterior portion of the pallidum produced a slightly cribriform appearance. There was a slight reduction of the medullary network of the pallidum, with thinning of the striohypothalamic radiations—the ansa system.

The ganglion cells of the corpus luysi, the nucleus ruber and the substantia niger appeared normal, except for occasional atrophy of an isolated ganglion cell.

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9. Winkelmann, N. W.: Progressive Pallidal Degeneration, Arch. Neurol. & Psychiat. **27**:1 (Jan.) 1932.

10. Hallervorden and Spatz: Eigenartige Erkrankung im extrapyramidalen System mit besonderer Beteiligung des Globus pallidus und der Substantia nigra, Ztschr. f. d. ges. Neurol. u. Psychiat. **79**:41, 1922.

CASE 2.—A man, aged 52, who had presented the typical picture of paralysis agitans for ten years, was affected with general rigidity and tremors of the paralysis agitans type, a parkinsonian mask, dysarthria and gait and attitude typical of this disease. Death occurred from lobular pneumonia.

Histologic study revealed well marked chronic atrophic changes in the large cells of the caudate nucleus and putamen. The small cells of the neostriatum were well preserved. Many of the cells of the globus pallidus were reduced in size, presented a rounded or angular appearance, and were filled with coarse, light yellow pigment granules. The blood vessels of this region showed evidences of arteriosclerosis, but without areas of softening or hemorrhage. The perivascular spaces were well marked in the globus pallidus and presented a slightly cribriform appearance. They contained dark and yellowish clumps of pigment granules. There was some loss of the medullary network of the globus pallidus, with a thinning of the striohypothalamic radiations—the ansa system.

In these two cases of presenile paralysis agitans the essential lesion was an atrophy of the large efferent cells of the neostriatum. The changes in the cells of the globus pallidus were less marked and may have represented merely secondary changes resulting from destruction of the superimposed efferent striatal system. There was a moderate degree of atrophy of the medullary network of the pallidum and the ansa system.

These cellular changes harmonized with my observations in the juvenile form of the disease, although they were of lesser degree. This I attributed to the comparatively short duration of the disease in both cases, seven and ten years, respectively. There were no gross vascular lesions, and the slight widening of the perivascular spaces and the moderate état criblé I did not regard as of essential pathologic significance.

C. and O. Vogt have laid great stress on an état criblé and état précriblé in the causation of paralysis agitans. Such changes, when marked, play a rôle in the arteriosclerotic forms, but I think that there is a risk in carrying this concept too far, a view which is shared by Dejerine, Jakob and Lhermitte. Especially is this true when there is well marked atrophy of the large cells of the striatum which, according to my view, represents an essential part of the efferent system of the corpus striatum and is in itself sufficient to produce paralysis agitans.

The characteristic symptoms of primary atrophy of the efferent neurons of the corpus striatum (striatal and pallidal systems) are: paralysis, rigidity and tremor. These symptoms may be secondarily induced by a variety of lesions. In many cases, especially of the senile type, both primary and secondary involvement of these systems coexist. The term primary paralysis agitans, however, should be reserved for the rarer system type of lesions in which primary atrophy and degeneration of cells is the essential lesion, thus harmonizing the pathologic changes in the striospinal with those in the corticospinal system.

I will now consider some observations of other investigators bearing on the question of primary paralysis agitans and its pathologic changes.

THE EFFERENT STRIATAL AND PALLIDAL SYSTEMS IN PRIMARY PARALYSIS AGITANS

Lhermitte and Cornil,[11] in their presentation of the pathologic changes of parkinson's disease at the Réunion Neurologique in 1921, recorded four cases belonging to the primary or cryptogenic form of this disorder, which they distinguished from secondary forms produced by encephalitic and arteriosclerotic changes. They did not subscribe to the opinion of C. and O. Vogt who referred the origin of this malady to an état criblé and état précriblé of the striatum and pallidum. They were struck by the fact that in Parkinson's disease the pathologic changes were not limited to any one region of the central nervous system. They found alterations in the cortex, the cerebral peduncles, the pons and medulla, and even in the spinal cord. These changes, however, were subject to great variations, but those of the cortex and the dorsal nucleus of the vagus were especially constant. To these, however, they did not attach significance in the explanation of the parkinsonian syndrome.

In all of their cases there were definite alterations in the substantia nigra. The cells were reduced in number, depigmented and atrophic, thus confirming the observations of Trétiakoff.[12] In order to prove the specificity of these lesions, they made examinations in a variety of other organic diseases of the central nervous system and found the substantia nigra similarly affected in nine cases, without, however, corresponding symptoms of paralysis agitans. They concluded, therefore, that these changes are not sufficient to explain the syndrome of paralysis agitans.

In their examination of the striatum, they found the small cells of this structure intact; the large cells, however, were reduced in number and size. The cellular changes were even more marked in the pallidum, where they were also reduced in number. In addition to a numerical loss, the remaining cells showed lesions of the cytoplasm which was reduced in volume, the cells presenting a globular, rounded appearance, the Nissl granules being broken up and many filled with dark pigment granules.

The fibers of the strioluysian system, the capsule of the corpus luysi and the ansa lenticularis were reduced in number. In view of these diverse observations, these authors did not insist that paralysis agitans

11. Lhermitte, J., and Cornil, L.: Recherches anatomiques sur la maladie de Parkinson, Rev. neurol. **28**:587, 1921.

12. Trétiakoff: Contribution à l'étude de l'anatomo-pathologie du locus niger de la maladie de Parkinson, Thèse de Paris, 1919.

should be ranged with the system diseases but pointed out that the system most constantly and gravely affected is the striate system, including in this system not only the striatum and the pallidum but also their subordinate centers.

Foix,[13] on the same occasion, discussed the pathologic changes in seven cases of Parkinson's disease. In all he found lesions in the locus niger. In four cases in which the corpus striatum was examined from this point of view, atrophic changes were also found in the large cells of the striatum and the globus pallidus. These findings, he stated, were incontestable, but those of the striatum were less severe than were those of the pallidum. The vascular changes were not particularly marked. The ansa lenticularis and peduncularis and the strioluysian, strionigral and striohypothalamic fibers were reduced in number. He considered these changes in relation to pathogenesis as follows:

> Deux hypothèses, en effet, sont en présence. L'une envisage la maladie comme une dégénération systématique, une abiotrophie. C'est l'hypothésie de Ramsay Hunt; maladie de système.
>
> L'autre envisage la maladie comme le résultat de lésions régionales soit d'origine vasculaire (C. et O. Vogt) soit d'origine infectieuse comme l'avait pensé Dana. Ici le Parkinson devient une maladie de région.
>
> (Two hypotheses, indeed, exist. One regards the disease as a systematic degeneration, an abiotrophy. This is the hypothesis of Ramsay Hunt—a system disease.
>
> The other regards the disease as the result of regional lesions, either of vascular origin [C. and O. Vogt] or of infectious origin, as Dana believed. Here Parkinson's disease becomes a regional disease.)

In conclusion, he expressed himself in favor of the regional hypothesis with a possible infectious etiology, an encephalitis, and suggested that syphilis may play a rôle.

Lewy,[6] in a large series of cases, also emphasized the wide dissemination of senile atrophy in the central nervous system in paralysis agitans. Lesions are found in the basal ganglia, cerebellum, thalamus, vegetative nuclei, spinal cord and cerebral cortex. He emphasized, however, the greater degree of involvement of the cells of the corpus striatum, and the characteristic symptomatology, paralysis, tremor and rigidity, was referred to this region.

Jakob,[5] in his well known monograph, recognized two distinct groups of cases of paralysis agitans, one in which the parenchymal cells and fibers are affected, and the other in which such degenerations are secondary to arteriosclerotic changes. The former group he called genuine paralysis agitans. In case 8 of his series there was a marked diminution of the large ganglion cells of the striatum with preservation of the small cells. The large cells by actual count were reduced to a third of the

13. Foix, M. C.: Les lésions anatomiques de le maladie de Parkinson, Rev. neurol. **28**:593, 1921.

normal number; not a single large cell in this region showed a normal structure. The cells of the globus pallidus were also atrophic, but were not reduced in number. The cells of the nucleus basalis were also degenerated. There was some loss of cells in the corpus luysi and the zona compacta of the locus niger. There was loss of nerve fibers in both the striatum and the pallidum. The ansa lenticularis, the lamella pallidi externa and Forel's H1 and H2 were atrophic. There was also reduction of medullated fibers in the corpus luysi, the locus niger and the capsule of the red nucleus.

In addition to these changes in the striopallidal mechanism, widespread degenerative changes of variable character were noted in the ganglion cells of other regions of the central nervous system, the cortex, the 'tween-brain and midbrain and the medulla oblongata.

Jakob concluded from his investigations that the most constant changes in genuine paralysis agitans are in the large cells of the striatum. The cells of the globus pallidus are less severely affected, and only rarely the substantia nigra.

The histologic changes are of a degenerative character and resemble senile degeneration of the central nervous system. He stated that vascular changes and consecutive focal lesions are not an essential pathologic substratum of this disorder but are not uncommon complications. In this respect there is a resemblance to other senile processes in the nervous system. He emphasized the other type of paralysis agitans which is secondary to arteriosclerotic changes, which Foerster [14] has designated the arteriosclerotic *Muskelstarre*.

From these studies it would appear that Jakob regarded the disease as a widespread degenerative disorder of the cells and fibers of the central nervous system of obscure origin, but resembling most closely the group of the senile degenerations, although senile plaques and senile fibrillar changes are commonly lacking. This degeneration is especially marked in the striopallidal mechanism, which underlies the essential symptomatology of paralysis agitans.

His description clearly shows that there is a preponderance of degeneration of both the efferent striatal and the pallidal systems in this type of disorder, although the degenerative process involves other cells not directly concerned with paralysis agitans.

Keschner and Sloan,[15] in a case of idiopathic paralysis agitans, also found degenerative lesions in the neostriatum, pallidum, thalamus, red

14. Foerster, O.: Die arterio-sclerotische Muskelstarre, Allg. Ztschr. f. Psychiat. **66**:902, 1909; Zur Analyse und Pathophysiologie der striären Bewegungsstörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:1, 1921.

15. Keschner, M., and Sloan, P.: Encephalitic, Idiopathic and Arteriosclerotic Parkinsonism, Arch. Neurol. & Psychiat. **25**:1011 (May) 1931.

nucleus, substantia nigra and locus caeruleus. The lesions were of a chronic degenerative nature, with état criblé, but no vascular proliferation and only slight glial proliferation. Their description shows clearly that in this type of the disease (genuine paralysis agitans) there is a preponderance of cellular atrophy and degeneration in the efferent neurons (striatal and pallidal) of the corpus striatum, although widespread degenerative changes are observed in cells of other regions not directly concerned with paralysis agitans.

They found that all of the large cells of the neostriatum and globus pallidus are destroyed or in various stages of atrophy. The small cells of the striatum are well preserved. In discussing these changes, they made the statement: "It is noteworthy that in the pallidum and the neo-striatum the large cells are most involved."

Here again, in idiopathic or genuine paralysis agitans the essential lesion is an extensive atrophy and degeneration of the large cells of the efferent striopallidal mechanism, more particularly affecting the large cells of the striatum.

COMMENT

A review of the literature since the publication of my study of primary paralysis agitans of presenile type shows that such cases are by no means rare. The characteristic lesions of the efferent striatal and pallidal cells are, however, frequently associated with similar atrophic changes in the cells of many other parts of the central nervous system. The disease process is therefore a widespread one, but with the greatest degree of concentration on the efferent cells of the striopallidum. Jakob and Lewy regarded this form of cell atrophy as allied to senile degeneration.

The characteristic motor syndrome of paralysis agitans, however, is directly referable to involvement of the large striopallidal cells and should be regarded as a primary degeneration in contradistinction to the secondary degeneration which follows so frequently vascular and inflammatory lesions.

The question of the locus niger has been much in the foreground since the investigations of Trétiakoff and the frequent involvement of this structure in encephalitis. In Lewy's series of fifty cases of paralysis agitans, the locus niger was found involved in association with the striopallidal lesions in only nine.

There is no question as to the occurrence of the syndrome of paralysis agitans after lesions of this region. This, however, is not surprising when one considers that the locus niger is a subordinate part of the striopallidal mechanism, and that important connections pass to this nucleus not only from the globus pallidus but also from the striatum.

Furthermore, the investigations of Spatz[16] showed that the zona reticularis of the locus niger is phylogenetically related to the globus pallidus. The locus niger also has important efferent connections with the extrapyramidal system.

It is therefore not surprising that lesions in this region should give rise to the symptoms of paralysis agitans, as it is an integral part of the striopallidal mechanism.

THE RELATION OF THE PARALYSIS AGITANS AND CHOREA SYNDROMES TO THE CELLULAR SYSTEMS OF THE CORPUS STRIATUM

In my original study of the different neostriatal and paleostriatal systems, two fundamental syndromes of the corpus striatum were postulated, based on a selective degeneration of the small and large cell systems in Huntington's chorea and paralysis agitans. In Huntington's chorea, the small cells are destroyed, with preservation of the large cells, while in paralysis agitans the conditions are reversed, the large cells suffering destruction with preservation of the small cells. The small cell system of the striatum I therefore identified with the syndrome of chorea and the large cell systems of the striatum and pallidum with the syndrome of paralysis agitans.

Many of the large cells of the neostriatum are giant cells and were regarded as the homologs of the cells of Betz in the cortex-like structure of the striatum. I believed them to be neopallidal cells in the neostriatum, subserving a function higher than, but similar to, that of the pallidal cells of the paleostriatum, and included both systems in my efferent pallidal system of the corpus striatum.

Subsequent investigations, especially the researches of C. and O. Vogt,[4] Bielschowsky,[17] Jakob,[5] and Riese,[18] have added materially to knowledge of the finer histology of this region.

These studies have shown that the large cells of the striatum and the pallidum, while related physiologically, differ in histologic structure and belong to separate anatomic systems. These investigators believed that the large cells of the striatum are not motor but serve a receptive and coordinating function, acting on the purely motor system of the globus pallidus. Their axons terminate in relation to the pallidal cells (striopallidal fibers). Originally it was thought that all of these fibers had this termination, a view which was subsequently disproved by Riese

16. Spatz, H.: Zur Anatomie der Zentren des Streifenhügels, München. med. Wchnschr. **68**:1441, 1921.

17. Bielschowsky, M.: Einige Bermerkungen zur normalen und pathologischen Histologie des striären Systems, J. f. Psychol. u. Neurol. **25**: 1919.

18. Riese, W.: Beiträge zur Faseranatomie der Stammganglien, J. f. Psychol. u. Neurol. **31**:81, 1924-1925.

who found many fiber connections passing through the pallidum to the subjacent centers of the substantia nigra and the red nucleus. C. and O. Vogt had already demonstrated a connection between the neostriatum and the corpus luysi. The terms striatal and pallidal are therefore preferable to neopallidal and pallidal, which I used to designate these efferent systems of the corpus striatum.

In interpreting the function of the efferent striatal cells, however, I would again emphasize their common involvement with the pallidal cells in paralysis agitans, their efferent and projection character and their physiologic and anatomic relations with the pallidum and infrapallidal centers as evidence of their motor function. And above all, I would emphasize their relationship to the syndrome of paralysis agitans. Loss of these cells, in both system and regional lesions, produces paralysis, rigidity and tremor, a symptomatology which is definitely motor. It is therefore difficult to escape the conclusion that they represent a higher type of motor mechanism in the neostriatum, which acts on the lower pallidal and infrapallidal systems.

THE FIBER SYSTEMS OF THE CORPUS STRIATUM

The Striatum.—The small cells of the caudate nucleus and putamen belong to the Golgi type II and terminate in close relation to the large cells of this region. They are small association cells which originate and terminate in the striatum and exercise an inhibitory and coordinating influence on its large efferent cells.

The large projection cells of the striatum (Golgi type I) are efferent and give off fibers which terminate in the globus pallidus, and constitute the larger part of the efferent striatal system.

There are also other striofugal fibers which traverse the globus pallidus and terminate in the gray matter of the substantia nigra (tractus striomesencephalicus), nucleus ruber and corpus subthalamicum. Accordingly, the striatum has connections through its projection system with the pallidum, the substantia nigra, the red nucleus and the body of Luys, which confirms its close physiologic relationship with the pallidal and infrapallidal mechanisms. This is the efferent striatal system and is the seat of a selective atrophy in the system disease type of paralysis agitans.

The Pallidum.—The globus pallidus cells are also efferent projection cells belonging to Golgi's type I. Their axons pass to the nucleus ruber, the substantia nigra and the corpus luysi, and also to the nucleus of Darkschevich and the nucleus interstitialis of Cajal. The fasciculus pontis lateralis also originates in the pallidal cells.

In addition, there are efferent connections between the cells of the globus pallidus and the ventromedial nucleus of the thalamus; the tuber

cinereum and the nucleus campi foreli. The pallidum, therefore, has not only connections with important nuclei of the extrapyramidal system, the red nucleus, the substantia nigra and the body of Luys, but also with nuclei in the thalamic and hypothalamic regions, the latter possibly subserving a vegetative function.

This is the efferent pallidal system which is also the seat of selective atrophy in the system type of paralysis agitans. Together, the *efferent striatal* and *pallidal systems* constitute the essential motor pathways of the corpus striatum and underlie the syndrome of paralysis agitans.

THE SYSTEM SYNDROMES OF THE CORPUS STRIATUM

The first specific syndrome of the corpus striatum was that described by Cécile Vogt [19] in 1911, in which athetosis, rigidity, and pseudobulbar palsy were found associated with an état marbré of the neostriatum. The lesions in this disease are limited to the caudate nucleus and putamen, and consist of extensive destruction of ganglion cells associated with a thick network of medullated nerve fibers, producing a marmorated appearance. Madame Vogt believed that the neostriatum exerts an inhibitory and regulatory influence on lower centers which, when lost, causes a release of function with the appearance of athetosis.

In 1912 appeared Wilson's [20] classic study of progressive lenticular degeneration, which threw additional light on the function of these ganglia. This group of cases presented the symptomatology of paralysis agitans with the addition, however, of clonic and tonic spasms. In some cases there were choreo-athetoid movements as in Gowers' well known cases of "tetanoid chorea."

In Wilson's syndrome there was a mixed symptomatology consisting of paralysis and rigidity, associated with tremor and involuntary spasmodic or choreo-athetoid movements. This variegated syndrome is produced by a mixed lesion of the corpus striatum, involving both its cortex, the neostriatum, and its motor center, the globus pallidus.

The essential symptoms of the corpus striatum are therefore chorea, athetosis and mobile spasm with paralysis, rigidity and tremor of the paralysis agitans type.

In 1916 [1] I attempted to reconcile the varied symptomatology of this region with the system syndromes of the corpus striatum. The chorea syndrome, I found, was dependent on the small cells of the neostriatum; the paralysis agitans syndrome, on the large cells of the neostriatum and the pallidum, a concept which was based on cell changes in paralysis

19. Vogt, Cécile: Syndrome du corps strié, J. f. Psychol. u. Neurol. **18**:479, 1912.

20. Wilson, Kinnier: Progressive Lenticular Degeneration, Brain **34**:295, 1912.

agitans and Huntington's chorea. The large cell striatal and pallidal systems represent the essential motor pathways of the corpus striatum and control the automatic-associated movements of the extrapyramidal mechanism. When these large cells are destroyed there results the syndrome of paralysis agitans; when these are released by destruction of the small inhibitory cells the striatal motor mechanism is set free, with resulting choreiform movements. The chorea is a positive and the paralysis agitans is a negative symptom in the Hughlings Jackson sense.

I held that the Vogt and Wilson syndromes represent combinations and admixtures of these two fundamental cellular syndromes. A lesion of the neostriatum involving both the small cells of chorea and the large cells of paralysis agitans would produce the athetosis, rigidity and pseudobulbar palsy of the état marbré of Madame Vogt.

The occurrence of paralysis agitans, together with choreo-athetosis, tonic and clonic spasms, as in Wilson's syndrome, I referred to simultaneous involvement of both the small and large cells of the striatum and the large cells of the globus pallidus. The various types of Wilson's disease I thought to be dependent on differences in localization and degree of involvement of these cellular systems within the corpus striatum.

Since this view was expressed in 1916, there has accumulated a wealth of clinical and pathologic material bearing on this question, which has added materially to knowledge of the function and syndromes of the basal ganglia. In general, the evidence supports the views on system localization which I expressed at that time and which I still believe offer the method most suited for the elucidation of this complex problem in symptomatology.

In 1920, C. and O. Vogt, on the basis of a large series of cases, formulated regional syndromes of the corpus striatum. The lesions were both focal and diffuse, localized in the striatum, the pallidum and the striopallidum.

Their syndrome of the striatum is characterized by both excitatory and paralytic symptoms. There is striatal akinesis, i. e., loss of facial expression, of associated movements, of orientation, of position and defense movements and also of asthenia. There is incoordination of speech and of standing and walking. There is also substriatal hyperkinesis (pallidal), consisting of choreo-athetosis, mobile spasms, tremor, forced laughter and weeping, and grimaces, hypertonic states and occasional hypotonia.

The syndrome of the pallidum they characterized by the development of general rigidity.

The complex symptomatology of the regional syndromes of C. and O. Vogt includes all the essential characteristics of the system syndromes. Indeed, I regard them as representing fragments and combinations of the two fundamental cell syndromes of this region. The small cells furnish the choreiform element of the symptomatology, while the large cells are responsible for the paralysis, tremor and rigidity of the Parkinson syndrome.

I would particularly call attention to the combination of the symptoms of chorea and paralysis agitans in their striatal syndrome, the occurrence of general rigidity in their pallidal syndrome and the bearing it has on a further elaboration of my cellular syndromes which will be discussed later.

In 1923, Jakob, in a comprehensive investigation of extrapyramidal disease, also formulated syndromes of the corpus striatum from the regional point of view which were similar to those of C. and O. Vogt except that he placed the lesion of athetosis and dystonia in the pallidum.

Jakob's striatal syndrome is characterized by slight paresis, with both voluntary and involuntary movements: incoordination and loss of associated movements and acts, e. g., sitting, walking; bulbar akinesis; loss of facial expression, defense and orientation movements, and slowing and reduced extension of movement; also tremor and shaking movements; hypertonic states, variable hypertonia (mobile rigidity).

In adults, degeneration of the small ganglion cells of the striatum produces chorea, with a certain akinesis and hypotonia. Slight diffuse conditions of the striatum produce parakinesis. Special involvement of the large ganglion cells produces a rigid state.

In childhood (immature brain), striatal lesions produce athetosis with variable hypotonia.

Pallidal Syndrome.—Partial lesions produce athetosis and torsion movements with hypertonia. Instead of athetosis, there are occasionally complex rhythmic movements.

Extensive pallidal lesions produce complete rigidity, with a high degree of plastic tonus, often with contractures.

GENERAL COMMENT

On reviewing the various syndromes of the corpus striatum, it is clear that steady progress has been made in knowledge of the intricate symptomatology of this region. In many respects the regional syndromes of C. and O. Vogt and Jakob harmonize with one another. They differ, however, in one important respect. C. and O. Vogt referred athetosis and dystonia to lesions of the striatum, while Jakob attributed these movements to partial involvement of the pallidum. C. and O. Vogt regarded all of the release phenomena of the striatum as a pallidal manifestation,

including the tremor and coarse shaking movements. Jakob, on the other hand, regarded athetosis and dystonia as release phenomena from diseases of the pallidum, due to overactivity of subpallidal motor mechanisms. In other respects their views practically coincide.

Investigators, like Lewy,[21] who find that the large cells of the striatum are sometimes involved in Huntington's chorea also recognize the massive preponderance of the destruction of the small cells, and none denies their relationship to chorea. The same is true of the large efferent cells of the striopallidum in relation to paralysis agitans, which confirms the general principles underlying the relationship of the small and large cells of the corpus striatum to certain definite functions. While cases of primary atrophy of the striatal and pallidal systems are no doubt rare, a careful clinical and pathologic study of this group will add materially to knowledge of striopallidal function.

It will be of interest in the future to give special attention to the subpallidal nuclei in this group of cases. Naturally, slight changes in these ganglia may be only a secondary manifestation. Nevertheless, it is well to bear in mind the possibility of a primary disease which would also include the subpallidal mechanism.

There is a further differentiation which I would suggest in the relation of the syndrome of paralysis agitans to the large striatal and pallidal cells, and it is this: I would refer the tremor type of paralysis agitans to the large cells of the striatum and the rigid type to the efferent pallidal cells. This suggestion is made with some reserve, but the evidence I believe supports this point of view.

The regional studies of C. and O. Vogt and Jakob show clearly that some striatal lesions produce a shaking tremor and paralysis of higher automatic acts and movements with rigidity. It is known that chorea is the product of destruction of the small cells; therefore, any other motor symptoms in this region must by exclusion be dependent on the large cells of the striatum. Kleist,[22] in an analysis of the symptomatology of Parkison's disease, accepted in the the main my cell formulations but considered the tremor as a special, indeed as the sole, symptom of destruction of these large striatal cells.

Jakob, in his syndrome of the striatum, attached a special importance to the large cells in the production of rigidity. Both of these conceptions of the function of the large cells are, I believe, far too limited. These cells constitute the sole efferent neural mechanism of the striatum;

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21. Lewy, F. H.: Zur pathologisch-anatomischen Differential-Diagnose der Paralysis agitans und der Huntingtonschen Chorea, Ztschr. f. d. Neurol. u. Psychiat. **73**:170, 1921.

22. Kleist: Paralysis Agitans, Stammganglien und Mittelhirn, München. med. Wchnschr. **51**:1769, 1925.

therefore, the striatal symptomatology, exclusive of the small cell function, would be dependent on this striatal system. Such being the case, this would consist of paralysis of higher automatic and associated acts and movements, tremor and rigidity, in other words, what clinicans have recognized from time immemorial as the tremor type of this disease.

In the rigid type, the theory of paralysis agitans sine tremore, which according to this view is dependent on the efferent pallidal cells, again finds support from knowledge of symptomatology gained from regional localization. There is general agreement that lesions of the pallidum produce paralysis of the extrapyramidal type with marked rigidity and without tremor.

A recent study by Winkelmann of progressive pallidal degeneration also supports this point of view. Here a progressive lesion of the pallidum ran its course without tremor, the symptomatology being confined to the akinetic-rigid syndrome. It is true that it was not a pure system disease but one of regional involvement of all the neural structures, both afferent and efferent, within the pallidum. Nevertheless, it is significant that so circumscribed a degeneration, limited to the pallidum and pars reticularis of the substantia nigra, should run its entire course without tremor or choreiform manifestations. The pallidal rigidity of the arteriosclerotic *Muskelstarre* and of carbon monoxide poisoning also confirms this interpretation.

It is rather difficult to explain the disparity in the views of C. and O. Vogt and Jakob in the localization of athetosis. The nature of the lesions often makes exact histologic localizations difficult, so far as it concerns the involvement of the small cells of the striatum. As the lesions in Jakob's cases were situated near the junction with the striatum, it is possible that the small cells were involved or that some of the outer pallidal cells were under the small cell striatal control. Further investigation will be required to settle this point, and until more specific data are forthcoming, it is, I believe, safer to consider all release phenomena of a choreic or athetoid character as related to the small cell system of the striatum.

It should also be emphasized that in the regional method, where focal or diffuse lesions are localized in the striatum or pallidum, not only efferent pathways but also afferent systems are involved, as well as the cellular structures of the region, which may tend to confuse and complicate the symptomatology.

The system syndromes of the corpus striatum may therefore be outlined as follows: The small striatal cells are inhibitory and coordinating, and when they are destroyed chorea results. The large striatal cells are efferent, conveying impulses to the pallidal and subpallidal

mechanisms. When these cells are destroyed there results a tremor type of paralysis agitans, i. e., paralysis of higher automatic-associated acts and movements, with tremor and rigidity. The pallidal cells are efferent and motor, and when they are destroyed there is produced the rigid type of paralysis agitans, i. e., paralysis of automatic-associated movements of a lower type together with rigidity.

All regional syndromes, I believe, represent fragments and admixtures of these three systems in various degrees. Athetosis, dystonia, mobile spasm and various choreo-athetoid manifestations represent the association of chorea and rigidity from involvement of the small and large cell systems.

CONCLUSION

The points which I particularly emphasize are:

1. Paralysis agitans, as expressed in my original monograph, is not a disease *sui generis* but a syndrome referable to the efferent neurons of the corpus striatum (striatal and pallidal).

This syndrome may be induced by a variety of pathologic lesions, viz., primary atrophy, senile degeneration, and vascular, inflammatory and neoplastic lesions. Therefore, primary and secondary forms are recognized.

2. Paralysis agitans, like spastic paralysis, is a fundamental type of central palsy referable to the efferent striatal and pallidal systems. Primary paralysis agitans occupies the same position in the striospinal system as does primary spastic paralysis in the corticospinal system.

3. There is a primary system disease of the paralysis agitans type occurring in early life, associated with atrophy of the efferent striatal and pallidal systems—primary paralysis agitans (juvenile type)—primary atrophy of the efferent striatal and pallidal systems.

4. There is also a primary paralysis agitans occurring in later life associated with atrophy of the efferent striatal and pallidal systems, in which these lesions are a part of a more general cellular atrophy of senile character in other regions of the brain—primary paralysis agitans (presenile and senile types).

5. There are three system syndromes of the corpus striatum: 1. The chorea syndrome, which is related to the small cell striatal system. 2. A paralysis agitans syndrome, which is related to the large cell striatal and pallidal systems. This syndrome may be still further subdivided into: A tremor type of paralysis agitans, which is related to the large cell efferent striatal system, and a rigid type of paralysis agitans, which is related to the efferent pallidal system.

6. All regional syndromes of the corpus striatum—striatal, pallidal and striopallidal—represent fragments and combinations of these cellular systems.

Sex and Internal Secretions: A Survey of Recent Research. Edited by Edgar Allen. Price, $10. P. 951. Baltimore: Williams & Wilkins Company, 1932.

"Sex and Internal Secretions" presents a cooperative survey of recent advances in research on internal secretion in relation to sex, organized by Dr. Edgar Allen on the invitation of the Committee for Research in Problems of Sex of the Division of Medical Sciences, National Research Council. Each chapter is written by an outstanding contributor toward clarification of the particular problems discussed. Emphasis throughout is placed on experimental evidence. The plurality of methods of approach stresses the complexity of the problem and sharply delimits conclusions showing fundamental consistency from the great mass of conjecture and noncritical experimentation that has grown up around this subject. Points in most urgent need of further investigation are brought into sharp focus. Paucity of authoritative investigation is especially apparent in the sections dealing with man. The many problems associated with the psychobiologic and the psychiatric aspects remain practically untouched. The book is aptly dedicated to A. D. Mead.

Frank R. Lillie, in a "General Biological Introduction," emphasizes the fundamental dimorphism within species into male and female individuals. He stresses the need for distinguishing conclusions drawn from a study of sex manifestations in individuals, carriers of gametes, and conclusions drawn from a study of the gametes themselves. From an evolutionary standpoint, dimorphism of gametes is soon attained, there being no further sexual evolution of the gametes throughout the whole range of the Metazoa. On the other hand, the sexual evolution of the individuals that bear the gametes presents an amazing complexity. There is a period in development when the future sex of the embryo is indistinguishable, or a period of sexual indifference. But, in most groups of animals at least, nuclear determiners exist during this period that direct the development of characters in either the male or the female direction. A radical distinction must be made between sex determination and sex differentiation. In most cases the factors of sex determination are chromosomal and subject to the usual laws of mendelian inheritance. Two major mechanisms of sex differentiation operate in the animal kingdom. In one, best known in insects, the mechanism of sex determination is believed to act also as the mechanism of sex differentiation, there being an almost complete absence of control of sex characters by any extranuclear mechanism. In the other, as in

higher vertebrates, the mechanism of sex differentiation is taken over by extracellular agents, the male and female hormones. These, dependent for their origin on the endocrine cells first determined by the nuclear mechanism, are regulated in their operation by still higher controls, both endocrine and nervous. They provide greater lability than is found in insects with one set of controls for the entire life history. Whether the original determination of an individual is male or female, possibilities of either form of sex differentiation inhere in all developmental histories, so that every zygote is potentially hermaphroditic in vertebrates. Of all the sex primordia some are responsive only to the male hormone, others only to the female hormone. Only the male or the female form of any pair of sex characters is a "conditioned" sex character, the contrasting sex character being "unconditioned," in the sense of being the same as in the castrate.

GENIC AND ENDOCRINE FACTORS

Charles Haskell Danforth reviews data bearing on "The Interrelation of Genic and Endocrine Factors in Sex." In reviewing the whole field of sex manifestations, certain underlying features are seen to be common to all groups of organisms. There is considerable evidence to show that males and females in general have different metabolic rates, and some evidence exists that alteration of these rates may at times serve to regulate the expression of sexuality. Masculinity and femininity are expressions of a deepseated capacity of the protoplasm to react in either of two different ways. In most cases genic factors are almost certainly involved in the determination of this dimorphic potentiality. In many lower animals and in plants, however, environment may be considered the sex-controlling factor, since it is the variable which regulates the direction of reaction. There is, in these cases, no internal factor capable of directing the reactions into one of the channels which are already predetermined. Complete dependence on external factors for the determination of sex leaves the control of sex ratios in an unstable condition. The development of an internal control tends to make the individual independent of its environment. Internal control is mediated chiefly through chromosomes and endocrines. It appears that "sex-determining" genes produce their effects through an influence on cellular metabolism. Through an elaborate cytologic mechanism, the new individual is definitely biased in one or the other direction. The intensity of an environmental influence that will be required to counterbalance the chromosomal factors and "reverse" the sex varies greatly in different species. Endocrine control differs from genic control in

that it is elaborated outside the tissues which it chiefly influences. Sex development may be altered or "reversed" by properly modifying the environmental, genic or endocrine control. That dimorphic sexuality is really only the expression of different gradations in a single process is indicated by the occurrence of sex intergrades, which may be conditioned by environment, a too even genic balance, unusual endocrine relations or conflict between genic and endocrine factors.

GENETICS OF SEX IN DROSOPHILA

Calvin B. Bridges discusses sexual phenomena from the standpoint of the cytologic-genetic method of approach in a chapter, "The Genetics of Sex in Drosophila." The differential distribution to the zygotes of the X and Y chromosomes determines which individuals will become male and which female. The male is the heterozygote and the female the homozygote. Studies on the nondisjunction of the X-chromosomes showed that the Y has little to do with sex determination. Sex differentiation depends on the X-chromosomes, i. e., on the presence of one or two such chromosomes. Males without a Y, however, are universally and entirely sterile, and evidence has been presented to show that two or more genes essential to normal maleness are contained in the Y. The male parts in the majority of gynandromorphs are explainable by the hypothesis of elimination of one X-chromosome from an early cleavage cell of an XX female. Study of the cytologic relation in the normal sexes, in the intersexes and in the supersexes shows that these forms are based on a quantitative relation between qualitatively different agents, the chromosomes. The theory of "genic balance" emphasizes the cooperation of all genes which are themselves qualitatively different from one another and which act together in a quantitative relation or ratio. In chromosome constitution the intersexes differ from females only in that they have an extra set of autosomes, so that the autosomes are concerned with the determination of sex and are male-determining in their action. Evidence shows that in normal differentiation of sexes several differentiators in the X are acting together to produce the total sex difference.

EMBRYOLOGIC FOUNDATIONS

Benjamin H. Willier discusses "The Embryological Foundations of Sex in Vertebrates" from the standpoints of the morphology and the developmental physiology of sex differentiation. In the study of amphibians it was shown that no structural differences in the two sexes can be detected until after the development of the cortex and the medulla of the gonad rudiment. Then, if the indifferent gonad changes in the

male direction, the cortex or germinal epithelium gradually disappears as such; if in the female direction, the cortex undergoes a gradual thickening. Differences in development also occur in the medulla. Similar changes occur in Amniotes. However, the gonad rudiment, though morphologically, is not physiologically, indifferent to sex, as a grafted gonad fails to undergo sex reversal even in the presence of a host gonad of opposite sex. That sex hormones are concerned in the embryonic differentiation of sex characters is shown by the development of the freemartin, and the experimental production of sex reversal. However, a study of the time at which sex reversal begins indicates that the early differentiation of the gonad rudiment is independent of hormone action, but is dependent rather on genetic determiners of sex. Whether or not a germ cell differentiates into a male or a female sex cell apparently depends on its tissue environment. The cortex is a female differentiating system, whereas the medulla is a male differentiating system.

SEX DEVIATIONS, INVERSIONS AND PARABIOSIS

Emil Witschi, in a chapter on "Sex Deviations, Inversions and Parabiosis," emphasizes the bisexuality theory at the base of which lies the qualitative distinction between male and female factors in contrast to the metabolic theory of sex which is entirely quantitative in principle. The entire constitution of an organism or gamete includes both male and female potentialities, what appears to be the sex being only the dominant sex. Differences merely in the quantitative ratios of the male and the female gene-complexes are the basis of the inherited sex. Certain types of sex deviation are due to unusual heredity combinations resulting in a near equilibrium of male and female genes. On the other hand, developmental factors favoring or inhibiting one sex selectivity can bring about very similar deviations without changing the hereditary basis. Witschi gives illustrations of the influence of such developmental factors. In developmental gonochorists, localized inductors, ontogenetic age and environmental conditions are factors effective, in all probability, through influencing specific trophic conditions of the primordial gonads and the indifferent germ cells. In birds and mammals the segregation of the sexes through a symmetrical distribution of the determining genes is so well established that only extraordinary developmental conditions can cause deviations from the genetic sex. Examples of such conditions are afforded by abnormal medullary activity and cortical destruction. All true human hermaphrodites are genetically of the female hereditary constitution. It is concluded that sex reversal in human beings is caused by abnormal growth of regularly present mesonephric derivatives, espe-

cially rete ovarii or suprarenal cortex. This growth seems frequently related to previous destruction or temporary insufficiency of the ovarian cortex.

METABOLISM AND SEX

Oscar Riddle, in a chapter on "Metabolism and Sex," points out that males have a higher basal metabolic rate than the corresponding females in those species in which adequate studies have been made. This is true of homozygous males as well as of heterozygous males. Data, however, on the effect of gonadectomy on the basal metabolism, are, as yet, fragmentary, inadequate and somewhat contradictory. The influence of injected gonadal hormones on the production of heat seems to be small, but the work on this subject is not considered conclusive. Hemoglobin and erythrocyte values are consistently higher in males than in females. As the oxygen carriers of the blood vary with the oxygen demands of the tissues, their sex difference is interpreted as representing unequal oxygen demands of male and female tissues. Riddle contends that oxygen carriers reflect primary sex difference and contribute evidence for the metabolic theory of sex. Other blood and tissue constituents, such as are indicated by creatine excretion and galactose tolerance, are discussed as indicative of metabolic and sex difference. It is suggested that chromosomes or genes exercise their influence on developing sexuality by establishing higher or lower oxidizing rates, thus leading to maleness or to femaleness.

THE BIOLOGY OF THE TESTIS

"The Biology of the Testis" is reviewed by Carl R. Moore. In the majority of forms, seasonal periodicity of reproductive phenomena is prominent. What the actual modifying factors are in the control of the short waves of activity as well as in the annual waves have not been definitely determined. Nutritional and temperature factors are suggested as possibly playing a rôle. The endocrine function of the testis with its relation to the permanent or periodic external male character has been established. Changes of the seasonal sex characters are strikingly correlated with changes in the interstitial cell mass. The influence of testicular hormone in conditioning the secondary sex characteristics and psychic responses in amphibians, reptiles and birds is also discussed. Additional problems arise in the biology of the mammalian testis, some of which are concerned with inherent differences between species presenting continuous germ cell formation and species presenting periodicity. There are indications that periodic activity is regulated especially by hypophyseal function, but much remains to be explained. Testis hormone is important for some phase of the life cycle of the sperma-

tozoa but in what manner is not clear. Duration of motility of spermatozoa is decreased when the influence of testis hormone is withheld and the capacity to fertilize an ovum persists for a much shorter period than the capacity for movement. There is no acceptable evidence that vasectomy or vasoligation has any rejuvenating effect as claimed by Steinach. Germ cell production continues even in the entire absence of vasa efferentia. Interstitial cell hypertrophy does not follow uncomplicated closure of the vasa, and there is no evidence to indicate that hormone secretion is in any way modified by the operation. Subcutaneous and intraperitoneal grafts of testis have been successful, but differentiation of the gamete proceeds no farther than the spermatocyte stage. Differentiated spermatozoa appear only when grafts are implanted in the scrotum. This is in accord with the observation that when testes fail to descend from the abdominal position into the scrotum the animal remains sterile. Evidence is presented to support the conclusion that the scrotum is a temperature-regulating mechanism. It produces a localized environment cooler by a few degrees than other parts of the body, and such a reduced temperature is required for germ cell production in mammals. Evidence is quoted that normal spermatogenesis cannot occur in the absence of vitamin A or E. Sterility may be produced by subjecting the testis to the influence of heat, x-rays, mesothorium and beta rays of uranium. Confirmed alcoholic persons many times possess spermatozoa in diminished numbers or are entirely without them. It remains a problem whether testis hormone is secreted by the same tissue in different vertebrates. Testes may be intact, may be actively producing spermatozoa and may contain appreciable amounts of interstitial cells and yet may not secrete hormone. Cryptorchid testes have been found to produce as much as do two normal testes. The problem of the specific source of the testis hormone remains unsettled. There have been numerous ardent supporters, and numerous opponents, of the hypothesis that the interstitial tissue is the source. Germinal epithelium and Sertoli cells have also been claimed as sources. It has not even been determined whether the testis secretes more than one hormone or only one. The study of castration effects, of implants and of injection of extracts shows that testis hormones stimulate male reproductive accessories but are without effect on female reproductive accessories. Secretions of the hypophysis stimulated the testis to function both in germ cell production and in hormone secretion. Testis hormones have no direct effect on the testes of males or the ovaries of females, but they exert a depressing effect on the hypophysis which results in a diminished amount of the sex-stimulating factor available to the organism.

TESTIS HORMONES

Fred Koch, in a chapter on "The Biochemistry and Assay of Testis Hormones," discusses the extraction and action of testis hormones. A testis-hormone potency which acts on the secondary sex characters of the fowl and on the male accessory glands of the castrated mammal has been found mainly in testis tissue, blood and human male urine. The same physiologic activity has been reported as present in human female urine, ovarian extracts and certain plant extracts. Whether the substance obtained by extracting testis tissue is the same as that from male urine and the other sources remains to be determined. It is not yet agreed whether it is the same or another type of testis hormone that controls the pituitary gland. Observations involving the positive action of testis hormone preparations on metabolism, blood chemistry, hemoglobin content, catalase or oxidase distribution are as yet of doubtful value.

THE OVARIAN FOLLICULAR HORMONES

Edgar Allen reviews the work on "The Ovarian Follicular Hormone, Theelin; Animal Reactions." The follicles of the ovary secrete a hormone which functions, as in the case of the testis hormone, to maintain the accessory genital organs and the secondary sex characters in full functional condition. This hormone from the follicles has been isolated in crystalline form and given the name "theelin." Names used by different investigators for this active substance before it was crystallized include "ovarian follicular hormone," "folliculin," "estrin," "progynon," "menformon" and "thelykinin." This hormone is present in the ovaries of many animals and reaches a high concentration in the ovarian follicles. Its action alone is sufficient to explain the ovarian endocrine mechanism of the nonpregnant cycle in the rat and mouse. It may be injected subcutaneously, intramuscularly or intravenously, but oral administration is not efficient. The rat and mouse are most frequently used as test animals because of the brevity of their estrus cycle and the cornification of the vaginal epithelium, which provides a clear endpoint that can be studied in the living animal. The most important of the reactions to this hormone is a wave of growth in the accessory genital organs. The vagina, uterus, uterine tubes and mammary glands, especially the epithelial tissues, show a high incidence of cells in mitotic division. Following the wave of growth is a change in the contraction rate of muscular tissues and secretion of glandular tissues, these changes culminating in estrus. A decrease below the threshold value of this hormone results in a return of the accessory genital organs to the castrate or resting condition. The function in primates seems to be similar. Experiments on monkeys show that during the breeding season ovulation usually occurs on the thirteenth or fourteenth day following the

first appearance of the previous menses. Regular menstrual periods may occur without ovulation and the formation of corpus luteum. Injections of theelin cause a wave of growth in the vagina, uterus and mammary glands, which develops them to a condition similar to that of the normal animal during the interval between menstrual periods at the fourteenth to sixteenth day of the cycle, i.e., up to or a little beyond their condition when large follicles of preovulation size are found in the ovaries. Cessation of administration of theelin or decrease in dosage is followed in two or three days by menstrual hemorrhage from the endometrium. Sections of the uterus show that the endometrium has not developed to a full premenstrual condition. An additional hormone from the corpus luteum must continue the action begun by theelin to accomplish this result. Such development is not, however, essential for menstruation. Theelin, then, is the essential ovarian mechanism for controlling menstruation. As the principal function of theelin is to control the accessory genital organs, and since it has little action on the ovaries themselves, it is a temporary substitute rather than a cure for hypo-ovarian disorders. It is probable that this hormone can be expected merely to alleviate abnormal menstrual conditions or temporarily to adjust severe menopausal symptoms until it is possible for the endocrine system to recover its balance.

Edward Doisy discusses the "Biochemistry of the Follicular Hormone, Theelin." Two estrus-producing compounds have been isolated and characterized, theelin and theelol, the latter differing from theelin by a molecule of water.

PHYSIOLOGY OF THE CORPUS LUTEUM

Frederick L. Hisaw reviews the "Physiology of the Corpus Luteum." Two active substances have been isolated from extracts of the corpus luteum. One of these has been named "relaxin" and the other "corporin," "progestin" or "lutin." "Relaxin" injected into virgin guinea-pigs during estrus produces marked relaxation of the pelvic ligaments within from eight to twelve hours. This results from a synergistic relationship between theelin and relaxin. No such action in mammals has been discovered. The large spontaneous contractions of the uterus that occur during estrus under the influence of theelin are inhibited by corporin. Neither theelin nor corporin alone can condition the uterine endometrium for growth of decidual tissue. Theelin must act first and be followed by corporin. Progestational changes in the uterus also depend on a "one-two" sequence of the action of theelin and corporin, and when both hormones are present at the same time the physiologic result may depend on the quantitative balance between them. The secretion of the corpus luteum produces a physiologic condition of the

endometrium conducive to implantation and maintenance of the life of developing embryos. However, in guinea-pigs and human beings, the normal development of embryos may occur in the absence of corpora lutea.

THE MAMMARY GLANDS

Charles Wesley Turner reviews the work on "The Mammary Glands." The development of the mammary glands of all viviparous mammals may be correlated with changes in the ovary. The accelerated development of the ovary at puberty is associated with the first marked postnatal growth of the mammary apparatus. The ovarian cycle is reflected in cyclic changes in the mammary glands. Rapid hyperplasia of the mammary gland occurs during the first half of pregnancy. During the second half, the growth phase is gradually superseded by secretory activity of the epithelial cells of the lobules. Cessation of secretory activity is associated with a marked involution of the gland, and further growth occurs only with another cycle of reproduction. Experiments are reported which show that the growth of the teat and duct system is stimulated by hormones formed in the ovary during puberty. Injections of theelin in spayed females produces a similar degree of development of the duct system. The rapid and extensive hyperplasia of the lobules of the mammary glands which occurs during the first half of pregnancy is stimulated by the corpus luteum hormone, but only in the presence of theelin. A species difference seems to exist as to the need of the corpus luteum for the development of secretory activity in the second half of pregnancy. A distinct species difference seems to exist also in the relation of the anterior pituitary glands to lactation. In the rabbit, pituitary extract alone is effective in producing lactation; in other species theelin or a lutein extract may be required. There is great need for further studies of species differences and the effect of quantitative differences in the amounts of the various hormones.

PLUMAGE TESTS IN BIRDS

Lincoln V. Domm, Reuben Gilbert Gustavson and Mary John contribute a chapter, "Plumage Tests in Birds." The female type of plumage in the domestic fowl is dependent for its expression on the presence of the female gonad regardless of the sex of the soma; male plumage appears whenever the female gonad is absent. Varying combinations of male, female and intermediate feathers at any given time may be explained by fluctuations in the production of female hormone and the differential thresholds of various body areas to the hormone. The more rapidly growing regions require higher concentrations of female hormone for modification, and with adequate concentrations the regions of rapid growth rate require less time for modification and

so record the response more rapidly. Changes in plumage are paralleled by changes in the size of the head furnishings, which also are controlled by gonad activity. Investigations among numerous species have demonstrated three types of sexual plumage differentiation. In the first group, male plumage is unconditioned and appears in the castrates of both sexes, being inhibited in females by the ovarian hormone. In the second group, male plumage appears only in castrates, being inhibited in both sexes by the hormones of the ovary and testis so that no sexual plumage dimorphism occurs. In the third group, a female type of plumage occurs in both sexes and in castrates, being independent of gonadal hormones.

OVULATION; OVA AND SPERM IN FEMALE GENITAL TRACT

Carl G. Hartman reviews the work on "Ovulation and the Transport and Viability of Ova and Sperm in the Female Genital Tract." The prevailing view that the follicle wall ruptures when the intrafollicular pressure has reached a certain stage, and so discharges the ovum into the body cavity, is discussed, as are the various theories as to the cause of the increasing follicular pressure. Evidence is presented in support of the alternate view of ovulation as a growth process. According to this theory, "ovulation is not a cataclysmic process but a quiet opening of the follicle wall at the point where progressive cellular changes have taken place under adequate stimuli." The hormone of the anterior lobe of the hypophysis has an important rôle to play in the causation of ovulation, and a delicate hypophyseal-ovarian balance determines the number of follicles that shall rupture in a species or individual. Semination in mammals is conceded to take place in the ampulla, in the first half of the tube. Usually but a single sperm enters the ovum. The established teaching that the female possesses her full complement of ova soon after birth has been called into question. Oogenesis has been described as a cyclic phenomenon, and the brevity of the life span of ovarian eggs as well as of discharged eggs stressed. Unfertilized ova are absorbed in the tube or uterus. The mechanics of the transfer of the egg from the ovary to the tube, whether by ciliary or by muscular action or by movements of the viscera, is still surrounded by uncertainty. The mechanical factors in the abdominal migration of ova also remain to be determined. Evidence is presented to support the theories of transport of the ovum through the tube by the ciliary mechanism or by muscular activity. The muscular quiescence of the tubes, induced by the discharged follicle, has been offered as an explanation of the sojourn of the ovum in the tube. The numerous factors which may operate in the transport of sperm in the cervix are discussed. Fertile insemination may be effected in the

presence or absence of a vaginal plug. Additional study is needed of the functions and behavior of the cervix before, during and following coitus. Muscular action of the uterine wall seems to constitute the chief factor in the transport of spermatozoa through the uterus in animals studied. Hartman emphasizes Parker's theory of the transport of spermatozoa through the uterine tubes. The tubal trabeculae break up the cavity into a system of longitudinal compartments in which eddies are formed as a result of which sperms are transported in a somewhat accidental way up or down the tubes. Evidence is presented that indicates that current statements of the long life of spermatozoa in the human female genital tract are incorrect, the spermatozoa being very short lived. While the doctrine of telegony has been adequately disproved, evidence suggests that spermatotoxins may be developed which may play a rôle in sterility in females.

ANTERIOR HYPOPHYSIS

Philip Edward Smith reviews "The Effect on the Reproductive System of Ablation and Implantation of the Anterior Hypophysis." The anterior hypophysis is essential to the structural and functional maintenance of the gonads and through them affects the other reproductive organs. In adult female rats, degeneration of the follicles occurs after hypophysectomy. The uterus becomes threadlike, and the vagina is reduced in size and cycles disappear. In immature males, removal of the hypophysis causes a decrease in the size of the testes and prevents the formation of spermatozoa. In adult males, degeneration of the seminiferous tubules, and apparently of the interstitial tissue also, occurs. Implants of an anterior lobe in immature females induce changes identical with those that occur at normal puberty, except that the number of mature follicles or of corpora may be greatly in excess of the number normally formed. Indirectly through the stimulation of the secretion of the follicular hormone the accessory genital organs also take on the appearance of maturity. There is not an accompanying general somatic maturity, and apparently the corpora lutea fail to elaborate corporin essential to the sensitization of the uterus. Implants of anterior lobes in immature males lead to a marked enlargement of the seminal vesicles and other parts of the reproductive tract, and some report hypertrophy of the interstitial tissue of the testis. Periodicity in the sex-hormone content of the pituitary is correlated with the estrual cycle. In hypophysectomized males, a replacement therapy restores the gonads to a normal structural and functional condition. In females, it induces follicular growth and the formation of cysts which later luteinize.

EXTRACTS OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

Earl Theron Engle reviews the "Effects of Extracts of the Anterior Pituitary and Similar Active Principles of Blood and Urine." There are two active gonadotropic principles in the anterior lobe, one causing luteinization of the follicle, the other causing follicular stimulation. When prolan A, the follicle-stimulating factor, is injected into immature female rats, enlarged follicles are found filled with fluid, the uterus is hyperemic and filled with fluid, the vaginal orifice is established and typical estral cells are present in the vaginal smear. When prolan B is injected into an immature mouse, the ovary is found, after an appropriate time, to be enlarged and hyperemic, with projecting luteinbodies with retained ova. The uterus is thin and unchanged, and the vaginal epithelium is unchanged. Premature development of spermatozoa in response to prolan has not been demonstrated, and the animals which have been treated do not mate. The discovery of Aschheim and Zondek of the presence in urine of pregnancy of substances resembling the active factors in anterior pituitary has given rise to numerous pregnancy tests. These are based for the most part on the development of corpora lutea or of hemorrhagic follicles in immature female mice following the injection of concentrated urine. The careful use of this method affords a diagnostic test which, in the hands of many investigators, appears to be about 98 per cent accurate. The differential diagnosis between hydatidiform mole and chorioma has been made possible by the quantitative assay of blood or urine as in the Aschheim-Zondek test. The great amounts of anterior pituitary hormone in blood and urine are regarded by the majority of investigators to be of placental origin though no decisive experiment has as yet been completed. While most investigators have spoken of two distinct active principles, the follicle-stimulating and the luteinizing, it may be that quantitative and temporal relationships vary the response. It is suggested that the physiologic state of the receptor organ rather than the nature of the active principle accounts for the dual response.

ENDOCRINE INTERRELATIONSHIP

Aura E. Severinghaus, Earl Theron Engle and Philip Edward Smith discuss "Anterior Pituitary Changes Referable to the Reproductive Hormones, and the Influence of the Thyroid and the Adrenals on Genital Function." Castration in either the male or the female produces histologic and gross changes in the anterior hypophysis which vary according to the species studied. It is generally agreed that the chromophobe represents an undifferentiated cell which may develop into either the acidophil or the basophil. The "castration cell" is a modified basophil and the pregnancy cell a new cell type derived from

the chromophobes. An increase in the weight of the anterior pituitary during pregnancy is associated with an increase in chromophobes and sometimes with a corresponding decrease in chromophilic cells and the presence of pregnancy cells. The potency of the anterior lobe is greatly increased by castration and decreased by pregnancy. Experiments on the injection of estrin indicate that the anterior-pituitary-gonadal mechanism is a reciprocal one. Few conclusions can be made as yet as to the thyroid-gonad relationship, though evidence indicates that the thyroid in some way inhibits or antagonizes the action of estrin and the male sex hormone. Experiments on the effect of the ablation of the suprarenals on the reproductive organs remain contradictory.

SEXUAL DRIVE

Calvin Perry Stone reviews the methods and results of studies on "Sexual Drive." Methods of study were grouped as follows: "(1) frequency of response methods; (2) balance or contrast of motives methods; (3) presence or absence methods; (4) self-observation and (5) standardized test procedure." Studies on the strength of drive by the frequency of response method in birds led to the conclusion that a strong copulatory drive is associated with immediacy of copulation and a weak drive with delayed copulatory response. The need is stressed for a genetic study of the rise, the maintenance and the decline of sexual drive in animals from the age of puberty to the senium, and for a correlation of this with work on endocrine changes. Recalled frequency of sexual intercourse in man cannot be considered, as yet, a satisfactory indication of sexual drive. Studies of activity as measured by the revolving drum, such as was used by Slonaker, Richter and Wang, revealed peaks of activity coming in from four to five day periods in female rats. Mating and vaginal smears show that spurts of activity coincide with copulatory willingness on the part of females. In females these cycles of activity appear at puberty and disappear following castration. In males, there is no periodicity of activity, no spurt at the onset of sexual maturity and no sharp reduction after castration. Study of nesting activities in female rats shows a cyclic nest-building variation in the nonpregnant animal concurrent with the ovulation cycle, and a great increase in nest-building activity at the time of parturition. Inanition effects a definite reduction of sexual drive. Copulatory ability is retained for considerable lengths of time following castration by some individuals though there is considerable variability in this respect. The effect of total castration in man is greatly reduced if the gonads are removed any time before puberty. The mental masculinity-femininity test of Terman and Miles

measures the proportion of responses which may be classified as masculine or feminine, but makes no attempt to determine if the sex difference demonstrated is due to biologic or to cultural factors.

ENDOCRINE DISORDERS IN SEX FUNCTION IN MAN

Jean Paul Pratt discusses "Endocrine Disorders in Sex Function in Man." While the testis plays an important rôle in the development of the accessory genital organs and male secondary characteristics, it has not been proved essential to the maintenance of the mature state. The greatest handicap in the study of the endocrine function of the human testis is the lack of a satisfactory measure of activity. Satisfactory evidence of the influence of castration on the prostate, seminal vesicles, vas deferens and Cowper's glands is not available. Potent testicular extracts suitable for human use are not yet available commercially. There is not even a theoretical basis for expecting testicular extracts to offset the changes of senility, for gland extracts do not stimulate the gland itself. The spermatogenic and endocrine functions of the testis are dependent on secretion of the anterior lobe of the hypophysis, as is evidenced in many cases of hypophyseal tumors. That understanding of the pituitary-testes-prostate relationship may have practical value in the treatment of hypertrophy of the prostate is pointed out. There is clinical evidence to show that an increase in the size of the uterus follows the administration of theelin, though the response is variable. Theelin has no direct effect on ovarian function but may substitute to some degree for ovarian deficiency. Secondary amenorrhea may yield to the administration of theelin, though the causal relationship has not been established. Kraurosis vulvae has been relieved by treatment with theelin, as well as with thyroid hormone. Many of the apparent positive results obtained with the clinical use of theelin are explained on the basis of suggestion. Functional bleeding associated with hyperplasia of the endometrium, occurring near the menarche or the menopause, may be relieved by the use of anterior lobe sex hormone. Results in the treatment of amenorrhea with anterior lobe hormones have not been constant. Great care should be exercised in the use of extracts of the anterior pituitary until more is known of the extent to which such administration may carry follicle stimulation. Oral administration of thyroid has yielded more convincing results in the treatment of menstrual abnormalities than the use of any other hormone. Emphasis is placed on the importance of critical discrimination between subjective and objective results in building a firmer foundation for future study and sane therapy, but, in the meantime, the relief of objective symptoms by all means available, suggestive or otherwise, is justified.

VERA G. MATHER, Howard, R. I.

Abstracts from Current Literature

THE MEASUREMENT OF VISUAL ACUITY. R. J. LYTHGOE, Report of the Committee on the Physiology of Vision, no. 10, Medical Research Council, no. 173, London, His Majesty's Stationery Office, 1932.

The first of the special reports in this series (no. 104) was one on "Illumination and Visual Capacities" by the same author. The report under discussion gives the results of his further studies on the same subject. In the technical sense, visual acuity is the degree or ability of the visual apparatus to discriminate details in the shape of objects, and its measurement is commonly based on the ability to discriminate two points or sources of light as separate and distinct. A vast amount of research has been devoted to this subject, dealing with such subjects as central and peripheral fixation and adaptation. The results from these studies have been of great value and are fundamental for carrying out more complicated methods of research.

It must not be forgotten that visual acuity as seen in every day life is not so simple a problem as visual acuity in the technical sense. For instance, the discrimination of two points is by no means the most sensitive form of visual discrimination. Discrimination of contour involves a much more complex process, and the form of vision is at least as dependent on the discrimination of contour as on visual acuity.

The work on the measurement of visual acuity outlined in this report is subdivided into several subsections. In the first and second sections are discussed the general physiology of visual acuity, the outlining of the problem and the apparatus that was used; in the third part, the results of the experimental work; in the fourth section, the factors influencing visual acuity, with the rôle it plays in illumination, and in the fifth section, the use of test types. The fifth section has an appendix which will be considered here in a little more detail. The report includes, in addition, a subsection by E. S. Pearson, which is a statistical analysis of the readings in the experimental work; a detailed summary follows this section. The tables of the experimental work are then considered, and at the end there is a complete bibliography.

Several important points which are made in the introduction should be included in an abstract even as brief as this. The author emphasizes that there are certain psychologic factors which must be considered when optic nerve impulses are under investigation. These lie between the optical image on the retina and the sensory nerve impulses. The optical resolving power of the eye alone does not determine the acuteness of its perception for detail and for shapes and contours. There must be some criteria of measurement. Three outstanding points are at hand for this. They are the minimum visible of the retina, the minimum separable and the minimum legible. They can be briefly described as follows: A visual task involving judgment as to the presence or absence of a white dot on a black background is a test for the minimum visible. If the task is to distinguish between one dot and two lying close together, it is a test for the minimum separable. If, on the other hand, the white area is of a complicated pattern, accurate description of which is necessary, the task is under the heading of the minimum legible.

Further, there are three separate types of physiologic processes which enter into this study—the three types of visual discrimination already outlined. One can speak of them as grades of perception. The first is the visual sense of position, which is the criterion of the minimum visible. The second is the visual resolving power, which is the criterion of the discrimination of two points, and the third is the form sense criterion, which must be the description of complicated shapes.

Another very important point in discussing factors on visual acuity is that of illumination. Beyond a physical and proportional increase in the brightness of

the retinal image, illumination can produce only small effects on the physical side, and it has never been shown that illumination per se has a psychologic action. It may be expected, however, to produce profound effects on the physiologic processes. It therefore has important theoretical as well as practical bearings on visual acuity. König's classic work shows clearly that visual acuity varies as the logarithm of the illumination and continues to increase up to high illumination.

The theory of visual acuity itself has given rise to many interesting and controversial findings and views. Visual acuity is usually measured by the reciprocal of the angle visually separable. It was once thought that two lines separated by 1 minute of visual angle appear discrete. Geometric optics show that the images of such points must lie 0.0043 mm. apart. This corresponds to a distance slightly greater than the diameter of one foveal cone. It was therefore thought that in order for the eye to resolve two dots or lines, their images must have an unstimulated cone between them. Later it was found experimentally that in the recognition of more complicated objects, such as letters of the alphabet, it was possible to do so when the details of their construction subtended 1 minute of visual angle. In turn it has been vigorously denied that the angular measurements of a letter are made use of by the retina in the recognition of that letter.

Vierordt said that the area of the details is the important factor, and Basler said that it is the general shape of the letter. Broca and Sulzer attempted to differentiate the retinal and cerebral components in a visual perception by studying the differences in the recognition of the letter V from the much more complicated letter E. Guillery would abolish the use of the term visual acuity, because in practice it is measured by the minimum separable. His claim is based on the fact that the theory of acuity tends to be based on two misconceptions, the first concerning the use of geometric optics, and the second on inadequate experimental data, resolution at angles much less than 1 minute being possible.

Hering's views on the relation between the discrimination of brightness differences and the reciprocal action of the retina have been applied by Hofmann to the effects of illumination. Wilcox' views are based on spatial induction, i. e., on simultaneous contrast. Hecht's theory is almost entirely concerned with the effects of illumination on the retina, and he has little to say concerning the form of the retinal image. He believes that all the retinal cones have different thresholds. When the illumination has increased, the number of cones in action are increased. The greater the population, the finer is the effective retinal mosaic. Houston has worked on this same line, but he apparently ignores the most fundamental property of sensory nerve endings, namely, that the frequency of impulses varies with the intensity of stimulation.

Hartridge's theory is of great interest because it is capable of explaining the high acuity of the eye. It does so by taking into account the so-called optical imperfections of the retinal image, which are really not imperfections but phenomena associated with the wave form of light. According to Hartridge, the eye actually takes advantage of these imperfections. By a short step it is possible to extend the theory to explain the improvement of visual judgments with increase of illumination. His calculations take into account the diffraction and chromatic aberration of the optical system of the eye. He points out that the eye possesses great ability in the discrimination of differences in brightness. The ability to discriminate these fine differences in brightness seems to be present, but quite irrelevant to that on which some theories insist, i. e., the presence of an unstimulated cone lying between two stimulated cones. When Hartridge used adjoining black and white rectangles, he found that when the line is shifted ever so slightly and by a distance represented on the retina by only a fraction of a cone, there will be a redistribution of the relative brightness falling on the retinal cones, and these changes in brightness will be noticeable.

Broca paid much attention to the passage of pigment between the cones which makes the grain of the receiving surface finer. The author believes that differences in brightness, i. e., a brightness difference threshold, and visual acuity are rather closely allied.

The only account to be included herewith relative to the apparatus is the fact that the author used wholly the Landolt broken circle, i. e., the letter C as a test type for his investigation. The use of this type of test object has been criticized on the grounds that it measures the light sense and not the form sense (Guillery, 1891). Unfortunately, no really satisfactory substitute has yet been found. The letters of the alphabet, although commonly employed, are probably recognized by the same sort of visual process as are simpler test objects. For instance, a C is distinguished from an O by the presence of a lighter area to the right of the ring.

It has been found that the relation between illumination and capacity to read a test object is not influenced by the form of the test object. They all give much the same result (Roelofs and de Haan, 1922). For instance, dots (Drault) give the same relation as letters of the alphabet.

In the immediate consideration of the results obtained, the first test included a graph illustrating a long series of readings taken, in which the size of the test object was varied and the number of mistakes made by the subject was measured at each size, the other experimental conditions being kept constant. From the graph the author desired to obtain reliable information for this type of experimental work. His discussion of this is entirely too long to be included here, but because of its bearing on all types of experimental work, the reviewer feels that it is well worth reading in the original.

The second subheading in the analysis of the results was the effect of illumination on visual acuity. From the graphs it was seen that an increase in the brightness of the test object had the effect of increasing the visual acuity. This increase is maintained up to the highest illuminations used, but the curve becomes slightly flattened at the top end. Over this limited range and with the conditions outlined, a definite mathematical formula relating visual acuity to the brightness of illumination was evolved. There have been considerable disputes about the illumination at which visual acuity is maximum, some putting it as low as 1 foot candle and others as high as 7,750 foot candles. These huge differences are probably due to the method of expressing results. It has been pointed out that in expressing results the logarithmic scale should always be used for illumination.

Looking at it from this standpoint, one can classify workers on visual acuity into those who work with a linear scale and get low values for the maximal brightness and those who work with a logarithmic scale and get a high value for the maximal brightness.

A discussion of uniform surrounds and visual acuity is the third subdivision. An error occurs here, which cannot be corrected, in that the increase of visual acuity with brightness of surrounds is masked to some extent by the progressive contraction of the pupil. It does bring out, however, that the greater effect of bright surrounds at high illuminations has an important effect on the visual acuity through the relation to the illumination. In other words, uniform illumination of the surrounds modifies definitely central visual acuity.

The subheading under glare continues to a certain extent the contradictory reports received from various workers, for in certain cases glare produces first an improvement and then, as the quantity is increased, a deleterious effect, which occurs in just the same way that increasing the surrounds above a certain value causes a lowering of visual acuity. It is probable, however, that sources of glare do not produce marked changes in visual acuity. This was illustrated nicely by the graphs which appear in the original paper.

The rôle of the pupil, the effect of its contraction and the consequent change in the optical system of the eye were investigated both by the wearing of artificial pupils and by photography of the pupil under the actual conditions of the experiment. Relative to this, it is possible to say only that some improvement in visual acuity is due to contraction of the pupil; that in the presence of glare the effects of the pupillary area on acuity play some part, and that in artificial pupils there is some fall in visual acuity due to the effects of glare surrounding themselves in such instances.

In the further brief discussion of test types there is one important point. The author so consistently found a 10 per cent error in the size of the letter and in

the dimensions of the different parts of the same letter that he considered the error the rule rather than the exception. Naturally, this makes comparison of records taken in different places almost useless.

In Lythgoe's discussion of dark adaptation, he found no constant effect as its result, and he was unable to confirm the findings of previous workers who have found that visual acuity, except for very low illuminations of the test objects, becomes worse during dark adaptation.

In general, the report is of the same high scientific standards as all of those that have been presented up to date by the committee on the physiology of vision. The reviewer considers it a most valuable addition to the physiology of visual acuity, and further, in several instances, feels that opinions expressed as a result of the experimental work are to be seriously considered as authoritative.

The methods, results, opinions and conclusions in the various sections are so compact that the entire work lends itself very poorly to a detailed review or to an abstract of the subject contents. Suffice it to say that it is one of the many reports from the Medical Research Council which must be read in the original for any satisfaction.

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THE LATE CONCUSSIVE SYNDROME IN CLOSED TRAUMATISMS OF THE SKULL: DISCUSSION OF THE REPORT. Rev. d'oto-neuro-opht. **10**:547 (Sept.-Oct.) 1932.

Borries called attention to the fact that "paradoxic vestibular reactions" (complete dissociation of the caloric and postrotatory reactions) have been frequently observed in syphilis and occur also in deaf-mutism, nonsyphilitic labyrinthitis and fistula of the labyrinth, as well as in cranial trauma. He thinks that the rotatory reaction proceeds from the semicircular canals, and that the caloric reaction is principally from the otolithic organs. Hennebert's syndrome is also observed in cases of traumatism of the skull.

Jentzer emphasized that these patients often have an organic basis for their symptoms, although it may be difficult to discover, since there are no pathognomonic objective signs of the concussive syndrome. Thousands of working men have been unjustly compensated for injuries. Seventeen cases in which the patients were reexamined after periods of from one to ten years are reported. Insurance companies should be liberal with these sufferers, since the effects of the traumatism may persist for ten or even twenty years after its occurrence.

Portmann believes that when there has been involvement of the cochleovestibular apparatus, it is impossible in most cases to know whether or not the trauma has caused small fissures in the petrous bone. Such fissures may result in osseous cicatrices or in connective tissue repair; the latter may constitute a preformed pathway for a later infection. The osseous cicatrization may be the starting point for a later development of otosclerosis.

Barré found 2 simulators among 96 patients. Of the 94 remaining, 25 were undoubtedly sincere. Barré hesitates to put a label on the other 72, but thinks that most of them correspond to the group called "psychopaths" by the reporters—patients suffering from an "involuntary reflex emotivity." A hypersensibility of the sympathetic nervous system is the commonest and most fundamental abnormal phenomenon in subjects of cranial trauma. Headaches occurred in 80 per cent of the cases. Reflex diplopia of vestibular origin, as well as diplopia from other causes, was noted. Muscae volitantes and visual obnubilation are due to vasospasm rather than to real hypertension. Vertigo was more frequent in cases without fracture than in those with it. The most important ocular disturbance was instability of the retinal arterial tension. When the mass of fluid injected intravenously is small, the temperature of the liquid has more influence than its hypotonic or hypertonic quality. Anisocoria was the most frequent pupillary anomaly observed; in all cases the reaction to light and in accommodation was normal. It is believed that the cause of the sympathetic disturbance is irritation of the sympathetic fibers in the dura mater. A small number of patients (after recovering from the accident), under the influence of overwork, emotion or prolonged care, suffer from a singular asthenia, a distaste for effort, continued heaviness of

the head, a tendency to diurnal somnia and nocturnal insomnia. Lumbar puncture reveals hypertension, and the removal of a quantity of the fluid is followed by rapid amelioration. Barré believes that the percentage of disability usually given is too high; he estimated from 10 to 25 per cent for cases of the first degree and from 25 to 50 per cent for cases of the second degree. As diagnostic acumen improves, physicians will become less satisfied with a simple diagnosis of concussion, and diagnoses more localizing and more in conformity with the actual pathologic change will be made.

Bujadoux reports his personal experience. He was injured in an automobile accident and was unconscious for twenty minutes. During the five following months he was perfectly well except that on looking downward he experienced visual difficulty and a distinct vertigo. This trouble was found to be due to paralysis of the oblique muscles, which Bujadoux believes was due not to a central lesion but to a disturbance of associated movements. He has observed this phenomenon in 3 other cases.

Weill suggests that one follow this method of examination: (1) Test for spontaneous angular deviation. (2) Test for inscription of deviation ("déviation inscrite") of the right and left hands in the principal positions of the head. (3) Test for angular deviation after two slow rotations (four seconds each). Normally, the deviation is in a direction inverse to the turning. If there is hypersensitivity, the deviation will be in the direction of the turning. If the deviation is unilateral, whatever the direction of the turning, there is vestibular asymmetry, imperfectly compensated. (4) Irrigate the ear with 10 cc. of water at 30 C. for ten seconds. Note the time of latency and then test the inscription of deviation for each hand. In the normal state the deviation is more marked in the hand on the side of the ear irrigated and is in the same direction. Four minutes after the irrigation, test for angular deviation. A normal subject deviates in the direction opposite the ear irrigated. By these methods a knowledge of the equilibration and orientation of the patient is obtained and one knows whether or not compensation is sufficient to permit him to return to his occupation.

Cossa thinks that encephalography is unreliable as a diagnostic measure, that the prognosis given by the reporters is too gloomy and that postponement of the estimate of disability does great harm by favoring the development of traumatic neurosis.

Lacat reports 3 cases with serious consequences following an apparently insignificant injury. In one, mental trouble developed; in the second, there was partial optic atrophy, and in the third serious visual disturbances with papillary edema occurred.

Puusepp mentions the following conditions of the brain as among the late manifestations: traumatic epilepsy, optic neuritis, abscess and traumatic cephalalgia. He has observed 3,000 cases of lesions of the brain and skull, in 121 of which the complications became manifest after several years. Of this number there developed 21 cases of recurring cerebral hemorrhage, 56 of epileptic convulsions and 24 of abscess. Death occurred in 6 of the first group, 1 of the second and 19 of the third. Among the cases of closed cranial fracture, there were 4 cases of abscess, 96 of epilepsy, 12 of optic neuritis and 9 of hemorrhagic pachymeningitis. Of 56 patients with open fracture who suffered from epilepsy, 2 died, 12 improved and 8 have had no attacks for five years. Of the cases of optic neuritis, decompression gave excellent results in 8. The results in hemorrhagic pachymeningitis were: 2 patients cured, 2 improved and 5 died. Abscess is much more frequent than one suspects, since, even during long periods, the symptoms are attributed to the traumatic lesions or to traumatic neurosis.

Coppez remarked in closing that the transitory diplopias that are observed at times form a part of the syndrome of giddiness and vertigo, and affect the whole oculomotor apparatus. The criticisms of Barré on the value of tonoscopy arise probably from the fact that his studies were made at a time when the technic was not so well developed. As to the percentage of disability, Coppez formerly agreed with Barré, but recent experiences have caused him to modify his views. It

may be that future progress in the study of the concussive syndrome will permit of its division into distinct types. Meanwhile, the idea of the "concussive syndrome" will render great service to physicians and experts.

Hicquet further remarked that few questions are more closely allied to otology, neurology and ophthalmology than this one. The suggestions of Weill are valuable. The otologic clinical picture is not pathognomonic but varies with the patient. Hicquet's experience does not accord with that of Borries with regard to the dissociation between the caloric and rotatory reactions. As Barré remarked, the otologic symptoms are accessory to the cerebral concussion; it is true that there can be no labyrinthine concussion without an accompanying cerebral concussion.

Martin added that in limiting the report to the late concussive syndrome it was essential to separate the pure concussive syndrome from that of "neuropath" or simulators. Psychology plays a rôle in the manner in which the subject of a cranial injury reacts. One indirect proof of the sincerity of the patients is the similarity of the description of the subjective syndrome by observers all over the world. Late infectious complications are rare in closed traumatisms. The quantity of air needed in encephalography varies with the case; from 25 to 40 cc. usually suffices to fill the ventricles satisfactorily, but sometimes 100 cc. or more is needed. Encephalography, like any other diagnostic measure, will not enable one to give the diagnostic key in all cases, but it is a valuable aid and its innocuousness justifies its use.

DENNIS, Colorado Springs, Colo.

SCLEROTIC ATROPHY OF THE CEREBRAL HEMISPHERES. A. PEKELSKY, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **34**:221, 1932.

A woman, aged 42, was admitted to the Wiener Versorgungshaus on Jan. 31, 1911, with the history that at the age of 2 years she had a febrile disease associated with cerebral symptoms resulting in spastic hemiplegia on the left side with contractures and occasional epileptiform seizures of short duration. In April, 1913, facial erysipelas developed, which lasted for twenty-six days. In December, 1917, the epileptiform seizures began to increase in frequency, and the previously poor mental condition became much worse; she became restless, very irritable, forgetful, suicidal and finally demented. She died in status epilepticus.

Macroscopic examination revealed an unusually small right cerebral hemisphere, with shrunken gyri but no microgyria or pachygyria; the leptomeninges appeared normal. On section the internal capsule and basal ganglia on the right side were atrophied, and there was a compensatory internal hydrocephalus on that side. There was no gross evidence of any congenital defect or of a focal lesion that could account for the pathologic process during infancy.

Microscopic examination revealed a degenerative process in the cortex of both cerebral hemispheres. There were no evidences of encephalitis. The development seemed to have been more or less arrested. The relatively slight disintegrations in various places in the brain resembled those ordinarily observed in chronic epilepsy. The reduction in the size of the right hemisphere could be explained histologically by: (1) a striking reduction of all layers of the cortex, (2) a considerable loss of the cortical fiber network and (3) cerebral shrinkage from degeneration of the white substance; this shrinkage was to a certain extent replaced by the hydrocephalus. It is noteworthy that the cellular degeneration and fiber defect in the apparently nonaffected hemisphere were of the same nature as those in the atrophied hemisphere, the difference being only quantitative.

In marked contrast to the general degeneration of nerve parenchyma and the diminution of the white substance, there was no striking replacement by fibrous glia. The glial reaction resembled that observed in the senile cortex and spinal cord. In some respects the glial reaction was not unlike that observed in sclerosis of the cerebellum, i.e., the systemic structure of the affected organ was retained in toto in spite of the general reduction of nerve cells, nerve fibers and myelin sheaths. There is no question that the glial reaction was secondary and that therefore the case cannot be included among cases of primary gliosis.

The absence of malformations or of any other developmental defects, such as porencephaly or marked hydrocephalus, and the presence of a sclerosing abiotrophy are, in the author's opinion, evidences that the entire anatomic process was a postfetal reaction. The history of an inflammatory process at the age of 2 years confirms this hypothesis. The generalized involvement of the cortex of both hemispheres, as well as the absence of any mesodermal reaction and of ependymitis, speaks against the likelihood of a disseminated process in the nature of encephalitis.

Pekelsky believes that in an acute process of the type that this patient had early in life the severe cellular destruction inhibits the normal development of the brain. He has no doubt that this case represents a more extensive type of lobar sclerosis, and that in such cases the general inhibition of the growth of the brain does not appear to be very definite because other parts of the brain become vicariously hypertrophied.

Pekelsky is unable to state definitely the primary cause of the pathologic process. The changes in the cortex resembled those of a senile involutionary process with secondary hydrocephalus and universal cerebral atrophy, a type usually observed in cases of endarteropathy of the small vessels due to toxic conditions. He therefore interprets this case as follows: Early in life there occurred some condition which produced endarteropathy of the small cortical vessels, followed by secondary abiotrophy of the cerebral cortex with secondary sclerosing glial proliferation which in the course of years became more and more intense. In such cases the volume of the brain depends, on the one hand, on its immanent tendency to growth and, on the other, on its limitation of growth owing to the sclerosing degeneration of the glia. The vital capacity of the plasmatic glial structure, which depends for its own existence on the living parenchyma, replaces, at least so far as volume is concerned, the loss of nerve parenchyma. It is owing to this replacement that in the case under discussion the less affected side of the brain in the presence of quantitatively similar changes presented so little evidence of apparent reduction in volume. The fact that the process is not limited to one half of the brain but affects both halves almost equally explains why in such cases the classic focal signs of predominating involvement of one side are so frequently overlooked and a bilateral process is suspected. The bilaterality of the changes also explains why so many of these cases are regarded clinically as genuine epilepsy.

KESCHNER, New York.

ACUTE NONSUPPURATIVE ENCEPHALITIDES IN CHILDHOOD. J. DAGNELIE, R. DUBOIS, P. FONTEYNE, R.-A. LEY, M. MEUNIER and L. VAN BOGAERT, J. de neurol. et de psychiat. **32**:550 (Sept.) 1932.

The authors describe a group of encephalitides associated with certain contagious diseases and eruptive fevers which have become notable in recent years. They believe that epidemic encephalitis has become much more rare since 1921; yet manifestations of acute encephalitis occur more and more frequently and are of poorly defined origin. One of the most common of these is postvaccinal encephalitis. The encephalitides following or associated with vaccination and infectious diseases are spoken of as parainfectious encephalitides. The authors describe a number of syndromes associated with these encephalitides: the convulsive syndrome, in which the convulsions may be generalized or focal, and are usually associated with fever, loss of consciousness and respiratory disturbances; a somnolent-ophthalmoplegic encephalitis characterized by somnolence, ocular paralysis and fever; a somnolent paretic syndrome characterized by somnolence and paresis of certain muscles, particularly of the muscles of the legs, and diminution or loss of tendon reflexes, and an irritative hyperkinetic syndrome, characterized by psychomotor agitation, fever and muscular contractions which simulate choreic movements. In the meningo-encephalitic syndrome, meningeal symptoms precede or coexist with encephalitic manifestations. Some infections described as serous meningitis may be of the meningo-encephalitic type. Finally, there is an encephalitic myelitic syndrome associated with bulbar and spinal changes as well as encephalitic mani-

festations. Parainfectious encephalitides have been recognized and reported but little understood, because of the paucity of histologic examinations. Complications following vaccinia are most frequent, but they not infrequently follow other infections, such as scarlet fever, measles, influenza and bronchopneumonia. Although the actual number of cases is high, the percentage is low; the vaccinal type, for example, occurs in 1 of 2,400 vaccinations. The occurrence in one member of a family of several persons fails to justify the term epidemic. The complications may occur in mild as well as in virulent cases, the symptoms of encephalitis appearing after the patient has recovered from the infection. In postvaccinal cases, the somnolent paretic syndrome often occurs. In smallpox, myelitis is more frequent than ataxia; in varicella, ataxia and myelitis, in the order named; in measles, apoplectic forms; in whooping cough, the convulsive form, and in mumps, the meningeal form. The onset of nervous complications may be acute and severe, or the symptoms may become progressively worse.

Vaccinal encephalitis has a high mortality (from 30 to 40 per cent), but few sequelae (10 per cent); measles has a low mortality (from 10 to 15 per cent), but frequent sequelae (40 per cent); in varicella the mortality and sequelae are both slight. Determination of the prognosis is difficult because patients with cases which seem particularly severe and are associated with coma may recover, while those with cases which at first show mild symptoms may die. In children of less than 1 year, vaccinal encephalitis is about one tenth as frequent as in children of school age. Nervous complications may appear about twelve days after vaccination; for varicella, from four to six days after the eruption; for measles, from the third to the sixth day, and for German measles, on the third or fourth day. The authors consider the possibility of a specific neurotropic virus as the agent of all parainfectious encephalitides and of the primary acute disseminated encephalitis; however, such a virus has not been demonstrated. All present similar histopathologic appearances, demyelinization and perivascular gliosis. The authors believe that the hypothesis of a specific neurotropic virus is not correct. They consider it possible that in smallpox, measles, German measles and chickenpox there may be an invasion of the nervous system by the organism of the disease. The toxic theory as put forth by Pedrau for vaccinal encephalitis has also been considered. The histologic lesions in the encephalitides of whooping cough appear somewhat different from those following the eruptive fevers. The possibility that these manifestations of encephalitis are the result of an allergic reaction is also considered.

The authors suggest the following classification of parainfectious encephalitides of children: (1) eruptive fevers with septicemic characteristics, vaccinia, measles, varicella and smallpox; scarlet fever and acute disseminated encephalitis might also be considered to belong to this group; (2) infections such as influenza, bronchopneumonia and neuritis; (3) whooping cough, and (4) the encephalitides following mumps. Mumps with neurologic manifestations is considered comparable to epidemic encephalitis and anterior poliomyelitis. WAGGONER, Ann Arbor, Mich.

VESTIBULAR DISTURBANCES IN CRANIAL TRAUMA: A STUDY OF ONE HUNDRED CASES. J. A. BARRÉ and G. GREINER, Rev. d'oto-neuro-opht. **10**:633 (Nov.) 1932.

It is on the examination of the vestibular apparatus that one must rely in order to determine the degree of incapacity and to estimate the sincerity of patients suffering from cranial concussion. The one hundred cases selected for this study were chosen because the observations were complete and comprised precise clinical and instrumental vestibular examinations, and because there were no previous pathologic conditions among them. In thirty, fracture of the skull was present. Late vestibular disturbances only are considered. In all cases of cranial concussion a complete vestibular examination should be made. Subjective vestibular disturbances consist of vertigo, uncertainty in the standing position, a sensation of inebriety in walking and pulsion. Vertigo was present in fifty-four cases—in 33 per cent of the group with fracture and in 40 per cent of the group without

fracture. Clinical signs of vestibular disturbances were observed in fifty-seven cases. Among the others, twenty presented no subjective or clinical vestibular troubles, but there were abnormal instrumental reactions. In the group with fracture, there were eighteen with clinical vestibular troubles, which were accompanied in twelve by subjective symptoms. There were twelve cases without clinical vestibular disturbances, of which six showed subjective symptoms. In the group without fracture, there were thirty-nine cases with clinical vestibular disturbances, of which twenty-one presented subjective symptoms. Thirty-one were without clinical vestibular disturbances; of these seventeen presented subjective symptoms.

The vestibular syndrome is incomplete in most instances. In twelve cases there were nystagmus, deviation of the arms and a positive Romberg sign; in eleven, nystagmus and deviation of the arms were present; four cases showed nystagmus and a positive Romberg sign; three presented deviation of the arms and a positive Romberg sign; in seventeen cases there was solely nystagmus; in seven cases deviation of the arms was the only sign, and in three cases a positive Romberg sign existed alone. The isolated signs, nystagmus and a positive Romberg sign, have different values. The former is of almost positive significance when properly investigated. The latter may result from the emotivity of the patient and may have only more or less typically the character of the vestibular sign of Romberg. All of the twenty cases with no subjective or objective clinical vestibular signs presented disturbed thresholds of excitation. In ten, hyperreflectivity or hyporeflectivity to the galvanic test was present. In fourteen, there was caloric hyperreflectivity or hyporeflectivity, and in twelve postrotatory nystagmus was markedly exaggerated or diminished. In no case was a complete and frank unilateral syndrome observed. It is important to employ all tests—galvanic, rotatory and caloric. A study of the data given in detail demonstrates that there is no parallelism between the complaints of the patient and the results of the examination. Patients with deafness from concussion almost never have vestibular disturbances of a corresponding intensity, and vice versa.

It is always a problem to know whether the complaints of the patient are exact. If there is a complaint of vertigo and disturbed equilibrium and no objective signs are discovered, a doubt of the existence of organic disease will arise in the mind of the examiner. In such cases it is better to assume a complete credulity and to give the patient enough rope to hang himself. In almost all cases the complaints of the patient have been well founded, the percentage of disability in recent cases being estimated at from 40 to 80. Often a later examination results in a lowering of these figures by 10, 20 or 30 per cent.

Good results from treatment with epinephrine or belladonna have been observed. These two drugs, of opposite actions, probably act as stabilizers, under different conditions, of the vasomotor function of the vestibular apparatus. In addition to medicines that influence the sympathetic system, rest in the country and avoidance of the cinema and of travel in trains and automobiles are helpful. In certain cases, bipolar galvanization through the mastoid processes has given good results. In cases in which headache coincides with an increase of vestibular disturbances, lumbar puncture has given relief.

DENNIS, Colorado Springs, Colo.

A CASE OF BILATERAL OCCLUSION OF THE POSTERIOR CEREBRAL ARTERY. F. G. VON STOCKERT, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **34**:23, 1932.

An infant, aged 15 months, was admitted to the clinic for nervous diseases in Halle with the following history: Birth and development were normal. At the age of 4 months the infant could sit up unsupported. At the age of 5 months convulsions appeared, which lasted all night, following which the infant was unable to sit up. Internal strabismus developed, with apparent inability to see objects in the left visual field. Examination on admission to the clinic revealed an unusually wide and flattened skull 46 cm. in circumference, 34 cm. wide and 33.5 cm. long. The child was unable to hold up its head or to sit or stand

unsupported. Attention could be attracted by auditory but not by visual stimuli, although the pupils reacted somewhat to light. There was no motor weakness, but all spontaneous movements were purposeless. The muscle tone was normal. The patellar and ankle jerks were lively, and there was no clonus. There was a bilateral Babinski sign, with preservation of the abdominal reflexes. During the examination frequent lightning-like generalized twitchings were observed. The fontanel was hardly palpable, and except for a distended vein at the root of the nose there were no evidences of venous stasis. Two days after admission, in order to relieve the hydrocephalus a callosal puncture was undertaken under narcosis produced by chloroform. The calvarium was unusually thin, and the dura was under markedly increased tension. As soon as the cannula entered the corpus callosum about 12 cc. of cerebrospinal fluid spurted out through the cannula, and an equal amount spurted out around it. The brain, which had not been pulsating prior to the escape of the fluid, then began to pulsate. Following this procedure the temperature rose. The infant died twelve days later.

Necropsy revealed hypoplasia of the suprarenal glands and parenchymatous degeneration of the kidneys. The calvarium appeared asymmetrical and bulged over the left frontal and parietal lobes, which were covered with extensive hemorrhagic pachymeningitis of long standing. The latter produced pressure on the subjacent cerebral substance. There were no evidences of an inflammatory process. The sinus transversus as well as the sinus sigmoideus contained fresh thrombi; the longitudinal sinus was completely occluded by a yellowish-brown thrombus which was adherent to the wall of the vessel. The brain showed aplasia of the occipital and temporal lobes on both sides.

Histologic examination disclosed cystic, sclerotic changes in the parts of the brain supplied by the posterior cerebral artery, i. e., the occipital and temporal lobes, but not in the thalamus. The temporal lobes were considerably affected, except the two upper convolutions, including the deeper opercular convolution and a part of the third temporal convolution, which were relatively well preserved on the left side. The lesions were much more extensive on the right side, where portions of the first, second and third temporal convolutions were severely affected; the lobulus fusiformis, the lobus lingualis (gyrus occipitomedialis and lateralis) and the gyrus hippocampi had completely disappeared, whereas on the left side considerable portions of the cornu ammonis were intact. Some of the caudal portions of the gyrus fornicatus were destroyed. The mesial portions of the occipital lobe were also severely affected. The pathologic process extended cephalad and mesially almost up to the splenium, which was only partly affected. Accordingly, the lobus precentralis was least affected, but the precuneus was more involved, so that its posterior portion, as well as the cuneus, was partially destroyed. As the lobus lingualis was also invaded, it may be said that the entire calcarine area within the lesion was affected. The lesions were of the nature usually observed in secondary degenerations following vascular occlusion.

KESCHNER, New York.

LATE OCULAR SYMPTOMS FOLLOWING FOCAL LESIONS IN CLOSED TRAUMATISMS OF THE SKULL. H. COPPEZ, Rev. d'oto-neuro-opht. **10**:647 (Nov.) 1932.

Traumatic retinal angiopathy (Purtscher) has been observed in cerebral concussion without direct ocular trauma. White spots appear in the internal layers of the retina and conceal radial hemorrhages, which are due to rupture of the perivascular lymphatic sheaths from sudden intracranial hypertension. The condition disappears in a few months but leaves, as a sequel, pallor of the temporal half of the papilla and a lunated scotoma.

Atrophy of the optic nerve follows violent blows on the frontal region or a bitemporal, crushing trauma. The nerve is bruised, broken or compressed, either by a fracture extending across the canal or by a momentary deformity of the latter. Partial or complete restoration of vision may occur after some weeks if the injury is slight. At times, progressive atrophy, due to an osseous callus, is observed.

Papillary stasis appears sometimes several weeks after a trauma and indicates an intracranial complication, such as hematoma, hydrops of the ventricles or encysted serous arachnoiditis. In cases of pure concussion, papillary stasis does not occur. Descending optic neuritis is usually caused by meningitis.

Several types of hematoma of the sheath have been observed: subdural hematoma of the sheath, in which the blood cannot spread in the subarachnoid spaces of the sheath; blood under pressure in the cranial cavity, which passes by the optic canal into the subarachnoid spaces of the nerve, and diffusion of blood into the nerve from rupture of an intratruncal vessel. The hematomas are frequently not accompanied by any functional or ophthalmologic symptom. When pressure on the nerve is great, blindness occurs; it disappears later, leaving lacunae in the visual field only if partial tearing of the optic nerve has taken place. In Grimminger's patient, blood entered the sphenoid fissure and spread along the ciliary nerves and the ophthalmic artery to within 15 mm. of the globe.

Lesions of the central optic pathways involve especially the chiasm, the optic tracts or the occipital lobes, and hemianopic signs are the result. If there is destruction of the visual fibers or of the cerebral substance, the condition is incurable and, if the lesion is from compression, hemorrhage or edema, it is curable.

Oculomotor paralyses occur for the most part immediately after the trauma, and recuperation is relatively frequent. Basilar paralysis can be overcome if the nerve is compressed or partially injured, but in the process of regeneration, the fibers may extend along other nerve trunks and produce Fuchs' syndrome. Nuclear paralyses are curable when caused by small hemorrhages, but late nuclear paralyses, due to degeneration or abscess, are incurable. The sixth nerve is most often involved. Involvement of the third nerve is rare and indicates serious intracranial disorder. Paralysis of the fourth nerve is due to tearing off of the pulley or to nuclear hemorrhage. Injury of the trigeminus may cause obstinate neuralgia or neuroparalytic keratitis. De la Farge described a facial syndrome, characterized by paroxysmal algias of the hemiface, often accompanied by reddening of the face, excess of tears and hyperhydrosis. Herpes zoster has also been observed. Paralysis of the facial nerve is frequent and, when it occurs late, is caused by inflammation and is often accompanied by otorrhea. Blepharospasm from irritation of the cortical center of the facial nerve has been noted. Involvement of the sympathetic is revealed by enophthalmos, facial hemiatrophy and other trophic disorders.

DENNIS, Colorado Springs, Colo.

THE FREQUENT APPEARANCE OF ENCEPHALITIS AFTER NONSPECIFIC TONSILLITIS. FANNY HALPERN, Jahrb. f. Psychiat. u. Neurol. **48**:154, 1932.

In the Vienna University Clinic for Psychiatry and Neurology the author observed six cases of encephalitis between the early part of September and the middle of December, 1931. The subjects were all women in whom the disease was a complication of tonsillitis. The encephalitic manifestations appeared early in the course of the sore throat. It is noteworthy that the encephalitis was in every case unusually benign. Thus far no fatality has occurred; four of the patients are on the road to recovery, and two have completely recovered. Obviously, the further fate of these patients cannot as yet be foretold. It is also noteworthy that the neurologic manifestations in every case conformed to the type designated by Redlich in 1917 as "encephalitis pontis et cerebelli," by Etter as "myelitis bulbi" or by Leyden as "acute ataxia."

Smears from the tonsils examined bacteriologically yielded no pathognomonic findings. Culturally, all cases showed the presence of pneumococci which were associated in two cases with Streptococcus haemolyticus and Staphylococcus aureus and in another case with a nonhemolyzing streptococcus. Cultures of the blood showed in one case, three weeks after the onset of the neurologic signs, Staphylococcus aureus and a nonhemolyzing streptococcus; in another case Staph. aureus was found in the blood six weeks after the onset of the tonsillitis. A bacteriologic examination somewhat later showed that the blood was sterile in every case. Unfortunately the spinal fluid could be examined bacteriologically only in one case, and here the results were not conclusive.

In discussing the etiologic relationship between the encephalitis and the angina the author adds nothing that has not been published previously. In the absence of data taken at autopsy and of thorough bacteriologic investigations of the spinal fluid she offers two hypotheses as to the etiology: (1) that there may be a causal relationship between the present increasing number of cases of encephalitis and the epidemic of tonsillitis, and (2) that there exists an epidemic of encephalitis due to an unknown virus which seems to have a special affinity for the brain stem and needs another factor to activate it, and that another infection such as an angina may be the activating factor in a person who had previously been resistant to the virus.

The paper is concluded with an addendum, which contains the clinical reports of two more cases of the same condition observed by Schlesinger in the third medical division of the Wiener allgemeines Krankenhaus during July and October, 1931. Both patients recovered.

KESCHNER, New York.

HISTOLOGIC LESIONS OF THE CENTRAL NERVOUS SYSTEM FOLLOWING EXPERIMENTAL INTOXICATION WITH THALLIUM. M. FRAULINI, Riv. di neurol. **5:** 526 (Oct.) 1932.

Because of the use of thallium in the treatment of tinea favosa in children and because general malaise and prostration, loss of appetite and, what is more important, sensory changes and weakness of the lower extremities accompany the treatment, Fraulini studied experimentally the reaction of nerve tissue to the administration of thallium acetate. He points out that, as far back as 1863, Sami had already reported on the lethal effect of thallium administered to animals, and that more recently Cortella, Leigheb, Roberti, Greving and Gegel and Schirder and Ugurgieri have reported on lesions in the central nervous system, as well as in the peripheral nerves, following experimental administration of the same metal. The literature concerning disorders in man following the use of thallium acetate as a depilatory is also reviewed. The death of fourteen children following symptoms pointing to toxic encephalitis in the Civil Hospital of Granada, Spain, in March, 1930, is recorded.

In his experiments, Fraulini administered thallium acetate by mouth in one toxic dose. The animal chosen was the dog, and the amount of thallium acetate administered was proportionate to the weight, the average being 55 cc. of a 1 per cent solution added to milk. On the following day the animals appeared apathetic, somewhat fearful and diffident and presented weakness of the foreleg which resulted in an uncertain gait. On the third day spastic paralysis was evident. The animals were very quiet and had diarrhea and vomiting. On the fourth day the hindlegs became entirely paralyzed and the animals attempted to drag their bodies. By the end of this day the animals died.

A histopathologic study of the spinal cord was made by the method of Nissl and Donaggio. With the Nissl stain the nerve cells showed chromatolysis; some cells appeared deeply stained, while others appeared as unstained shadows. In some cells the tigroid substance was conglomerated in small areas of the cytoplasm. The nucleus was displaced in many cells. With the method of Donaggio for staining neurofibrils, the intracellular neurofibrillar reticulum appeared consistently conglutinated, the fine reticulum having lost its normal netlike appearance and vacuoles being found among the fibers. In a few instances the reticulum was not stained. The nucleus appeared hyperchromatic and was often displaced toward the periphery.

FERRARO, New York.

A MYOPATHIC FAMILY WITH HYPERTROPHIC, PSEUDOHYPERTROPHIC, ATROPHIC AND TERMINAL (DISTAL IN UPPER EXTREMITIES) STAGES. STANLEY BARNES, Brain **55:**1 (March) 1932.

A most remarkable family, whose history dates back to 1749, with about 500 descendants, some of whom presented various forms of myopathy, which were

probably phases through which each member afflicted tended to pass, is excellently described. Four different stages occur: (1) The hypertrophic stage with true hypertrophy. Two cases are mentioned in which there was especial oversize of the calf muscles. (2) The pseudohypertrophic stage marking the decline in power. This was illustrated in 1923 in a girl aged 21. (3) Gradual atrophy with increasing weakness. This differs definitely from the Charcot-Marie-Tooth type of peroneal atrophy. (4) The terminal stage, with distal atrophy in the hands. A case recapitulating the four stages, with atrophy and weakness in all the muscles of the arm, is described. Histologic examination was possible in only one case; atrophic changes were found, increasing in intensity from the adductor magnus to the gastrocnemius and soleus muscles.

Although the diagnosis of muscular dystrophy seemed clear, the type was unusual, differing from the pseudohypertrophic form in direct inheritance, equal affection of both sexes, onset at an unusually late age, the distal type of atrophy and weakness of the upper extremities and the absence of lordosis. Of the clinical features, onset at a late age, from 35 to 50, in a large majority of the family was most unusual; also, the progress of the disease was slow. Of interest was the onset of the disease or a rapid decline in power following trauma or some intercurrent condition, which, however, were only precipitating factors. In only one case was there a tendency toward myotonic contraction. The early loss of the tendon reflexes has been notable in the recorded cases. There was a constant tendency to adiposity and a large build, with a remarkable absence of other defects. In the family studied, aberrant forms were exceedingly rare; other reports in the literature indicate that the formes frustes were of two kinds, one consisting of typical features of myopathy, the other of physical defects of a less specific type.

In an attempt to apply Mendel's laws to the family, it was found that the disease has been transmitted by males and females, who have been affected in about equal numbers, and that the inheritance is of a dominant type. Family studies of other authors are reviewed, but a definite conclusion in regard to the mode of inheritance was hardly possible. In general, however, it is concluded that muscular dystrophy is determined at the birth of the ovum. The family record, in which 160 descendants of the first patient were examined, is given.

MICHAELS, Boston.

TWO CASES OF CHIASMATIC HEMIANOPIA FOLLOWING NONPENETRATING CRANIAL TRAUMAS WITH LATE CONCUSSIVE SYNDROMES. C. DEJEAN and J. BONNAHON, Rev. d'oto-neuro-opht. **10**:670 (Nov.) 1932.

The first case was that of a man, aged 45, who, in June, 1931, complained of intense tinnitus, vertigo and complete deafness, which had begun three months previously. For eight months, vision had been failing until it had entirely disappeared in the left eye. The patient had been injured in 1914 by the explosion of a shell, but had no actual wound. He had the sensation of being crushed and was not oriented in time and space, and bilateral otorrhea appeared immediately. Examination revealed thickening and atrophy of the drum membranes, complete bilateral deafness and vestibular areflexia. Vision was lacking in the left eye and was reduced to 2/10 in the right eye. The visual field of the right eye presented a nasal hemianopia of irregular outline, encroaching above on the temporal field but respecting the central region. Other examinations revealed nothing abnormal except headaches and enlargement of the sella turcica. In the absence of endocrine disturbances, a neoplasm in the sellar or suprasellar region was assumed. Roentgenotherapy produced rapid improvement. Hypophyseal adenoma is the only new growth in this region that reacts so quickly to the roentgen rays.

The second patient was wounded in 1918 in the right side of the forehead by a projectile and was unconscious for three days. Bone fragments of the skull were removed at the time. Six months later examination revealed a left homonymous lateral hemianopia with a positive hemiopic pupillary reaction. Since then, late concussive symptoms had appeared, including headaches, vertigo and jacksonian epilepsy. The left hemianopia has progressively increased, encroach-

ing on the right field. The irregularity, asymmetry and inequality of the campimetric limits are essential signs of chiasmatic hemianopia. In this case the lesion was located in the right posterior horn of the chiasm. There were no signs of hypophyseal dysfunction. Explanation of the pathogenesis and the connection with the cerebral concussion is difficult. It is known that trauma to the skull causes cicatricial lesions that involve glial tissue and vessels, hemorrhagic lesions and vascular alterations. It is assumed that a small vessel in the retrochiasmatic region was ruptured, and that the resulting cicatrix compressed the posterior angle of the chiasm. An exudate or a meningitic process might also explain the visual alteration, but these signs were excluded by the history and by the fact that such a process would not have been so strictly limited as to affect only the posterior horn of the chiasm.

DENNIS, Colorado Springs, Colo.

CRIME AND THE ENDOCRINE GLANDS. LOUIS BERMAN, Am. J. Psychiat. **12:** 215 (Sept.) 1932.

The age-old problem of the cause and prevention of crime has finally been solved by Berman in certain and simple terms. The essential etiologic agent in breeding the criminal is the endocrine gland, a hypothesis which is supported by a priori principles and impressive tabular summaries. The endocrine glands regulate metabolism and therefore, Berman says, must regulate personality. He makes the astonishingly broad remark that "all those who investigated disturbances of personality with the apparatus of metabolism studies have found disturbances of metabolism." This wholly unsubstantiated generalization is the keystone of the paper. Berman sets out to prove by statistical study that ". . . the criminal personality is a resultant of an abnormal functioning of the endocrine glands." The criminals whose endocrine status was studied were found in the Classification Clinic at Sing Sing, while healthy and law-abiding persons constituted the controls. The results show an amazing amount of endocrinopathy among the criminals, but their significance is somewhat reduced by the author's failure to describe his standards of normal and abnormal function of the glands. Among the results reported are: basal metabolism in excess of plus 10 per cent in 30 per cent of the criminals and in 7 per cent of the controls; low blood sugar in 48 per cent of the convicts and in 12 per cent of the citizens; sella turcica ratios below average in 51 per cent of those who violated the law and in 22 per cent of those who obeyed the law; and endocrinopathy of some sort in almost every criminal studied. Even more remarkable is the relationship between the endocrine status and the type of crime; thus, the housebreaker is a hypopituitary type, the thief a hyperthyroid, the murderer a hyperthymus, the rapist a hypergonadal and the thug a hypersuprarenal type.

From the statistical data presented, Berman concludes that "endocrine disturbances occur at least from two to three times as frequently among the criminal group as they do in a control group. Also, that certain types of crime tend to be associated with certain types of endocrine imbalance." To solve the problem of crime, the author has a correspondingly simple solution; he suggests "great regional endocrine clinics in every portion of the United States, and preventive clinics where all children could undergo a periodic survey of the condition of their endocrine system." A great problem of many centuries has thus been happily solved.

DAVIDSON, Newark, N. J.

REMARKS ON A CLINICAL STUDY OF ACHLORHYDRIA. HENRY MOORE, Brit. M. J. **1:**363 (Feb. 27) 1932.

This extremely valuable paper might be divided into two parts; a study of achlorhydria in various conditions and remarks on nonmegalocytic anemia. Achlorhydria is not uncommon in otherwise apparently healthy persons, 4 per cent according to some authors, while in older people the incidence is much higher. It is frequent in pylorospasm. Among eighty-three cases of diabetes mellitus, the author found achlorhydria in 39.7 per cent. It was present in 78.7 per cent of a series of forty-seven definite cases of hyperthyroidism. In one hundred cases

of gastro-intestinal complaints, forty-five patients had such vague symptoms that no definite diagnosis could be made other than that of achlorhydria. There were seventy-four cases in a miscellaneous group including fourteen of pulmonary tuberculosis, two of which also presented chronic nephritis. There were thirteen cases of pernicious anemia and ten of cardiovascular hypertensive disease. Achlorhydria was much more frequent among females than among males. No definite hypothesis is advanced to explain this phenomenon.

Of the thirty-three cases of nonmegalocytic anemia of unknown origin with achlorhydria, twenty-seven were in females. The anemia was chronic in all, and in some had lasted several years. Frequent complaints were weakness, palpitation and breathlessness on exertion. Many patients complained of gastro-intestinal and digestive disturbances. Atrophic superficial glossitis was fairly common. Menstrual irregularity was not uncommon. The average color index was 0.66, and the average erythrocyte count 3,700,000 per cubic millimeter. The degree of the anisocytosis and poikilocytosis was usually proportionate to the degree of anemia. Oral administration of iron was the most effective therapeutic agent. Dilute hydrochloric acid did not seem to have any effect on the restoration of the blood, but did relieve the frequently associated gastro-intestinal symptoms. The administration of liver extract and desiccated stomach proved useless. Cooked whole liver by mouth gave doubtful results. In the maintenance of improvement both iron and acid seemed valuable, though the former seemed by far the more important. As to its etiology, the author believes that there are probably a number of factors, achlorhydria being an extremely important one.

FERGUSON, Niagara Falls, N. Y.

CERVICAL HYPERESTHESIA, APHASIA, MUTISM AND OLFACTORY HALLUCINATION FOLLOWING CRANIAL TRAUMATISM. G. DE MORSIER, Rev. d'oto-neuro-opht. **10**:682 (Nov.) 1932.

Two weeks after recovering from coma due to a fall on the head, a patient had violent pain in the occiput, neck and shoulders, with cervical hyperesthesia. The pressure of the spinal fluid, which was normal (30) at the time of the accident, was increased to 68. The hyperesthesia can be explained only by an unusual anatomic arrangement of the meningeal sheaths around the roots of the cervical nerves, permitting the accumulation of blood that caused irritation of the nerve roots.

Posttraumatic aphasia is rare. It is interesting that in the following case Wernicke's aphasia resulted from cranial traumatism. The patient suffered an occipital wound and was unconscious for days. The spinal fluid was hemorrhagic, and its pressure was increased (54). When the patient recovered consciousness, the naming of objects was impossible, and the simplest order was not comprehended. There were alexia, agraphia, paraphasia and jargonaphasia, generalized anesthesia, abolition of the abdominal and cremasteric reflexes on both sides and abolition of the right corneal reflex. Eighteen days after the injury the aphasia had considerably diminished, but memory was deficient for recent and old events.

Still considered at times a particular symptom of hysteria, mutism is met with in acute alcoholism, encephalitis and early dementia praecox. The following case demonstrated that it may result from cranial traumatism. A man, aged 45, after a fall that caused a wound in the left temporal region, was momentarily unconscious and then was unable to speak. He could comprehend everything and could express himself easily by writing. The mutism lasted six hours. Since then the usual sequelae of cranial concussion have appeared.

A man, aged 33, was struck on the left temple. Consciousness was not lost, but at the moment of the blow the patient smelled an odor of sulphur and saw flashes of light. He resumed work, but in half an hour violent pains in the head forced him to stop. Later he returned to work, but after six weeks the usual symptoms, headache, vertigo and ocular troubles, appeared, and he was obliged to cease. Such cases are rare, but they do exist.

DENNIS, Colorado Springs, Colo.

CYTOLOGIC REACTIONS OF SYPHILITIC CEREBROSPINAL FLUID AND A NEW METHOD FOR THE DIAGNOSIS OF NEUROSYPHILIS. J. JACCHIA, Riv. di neurol. **5**:499 (Oct.) 1932.

After having discussed the value of vital staining in establishing the entity and the type of cytologic reaction of the cerebrospinal fluid in neurosyphilis and the importance of plasma cells in the fluid, and after summarizing the various aspects and classifications of such reactions in connection with the various clinicopathologic aspects of syphilis of the nervous system, according to the views of French authors (Ravaut and Boulin), Jacchia discusses the new method for the diagnosis of neurosyphilis recently suggested by Luz in the *Comptes rendus des séances de la Société de biologie* (1932). The method consists of giving an intrathecal injection of 0.5 cc. of sterile double distilled water (following the previous withdrawal of 15 cc. of fluid) and taking another sample of the fluid twenty-four hours after the injection. Under normal conditions the water causes a meningeal irritation, with subsequent increase of cells in the fluid. This reaction, according to Luz, is less pronounced when a neurosyphilitic process is present.

Jacchia reports in detail his results in nine cases of neurosyphilis and in cases of nonsyphilitic involvement of the central nervous system; he states that following the introduction of water a true purulent aseptic meningitis may develop, with considerable modification of the cerebrospinal fluid and occasionally with serious symptoms. Among the symptoms that follow introduction of water into the cerebrospinal fluid, he mentions particularly increased pressure of the fluid, pain along the spine and the lower extremities, headaches, which at times are intense and may persist for three or four days, nausea and hyperthermia, which at times may be preceded by chills, profuse perspiration, a stage of anxiety, sometimes accompanied by delirium, tachycardia and occasionally collapse.

Jacchia finds that there is a certain resistance of the meninges of neurosyphilitic patients to the irritative stimulus of injected water, but that morphologically the cytology of the fluid in neurosyphilis is not substantially different from the cellular reaction in other conditions without syphilis; this does not uphold the diagnostic value of the method.

FERRARO, New York.

FAMILIAL PERIODIC PARALYSIS. EDWIN G. ZABRISKIE and ANGUS MACDONALD FRANTZ, Bull. Neurol. Inst., New York **2**:57 (March) 1932.

The authors present a detailed case study of a man, aged 23, presenting a severe form of familial periodic paralysis. The patient was a well nourished man, of good muscular development, without evidence of pseudohypertrophy of muscle groups. Systemic examination in the intervals between attacks gave entirely negative results. Chemical studies of the blood showed nothing abnormal although dextrose tolerance was slightly increased. The family history was significant. The maternal ancestry showed migraine in the two preceding generations, and the patient's mother had also suffered from what was presumably familial periodic paralysis. The patient's attacks started at the age of 7 years, occurred about twice a week and persisted for two or three hours and occasionally for a day or longer. After the age of 12 the frequency of attacks increased somewhat, and the duration decreased. Prodromal symptoms in the form of sensations of numbness or pressure over the back of the neck were usually present. Examination during an attack showed a decrease or abolition of the deep reflexes, slowing of muscular decontraction after reflex or electrical stimulation and reduction or loss of excitability of the muscles. At times an enlargement of the heart to the left with an apical systolic murmur was found. Partial attacks could be induced by local cooling, and recovery was artificially accelerated by local heating. Changes in electrical excitability could be followed during such experiments. Microscopic examination of muscle removed at biopsy showed a vacuolation of some fibers and in places a granular substance in these vacuoles. The authors demonstrated an unusual fluctuation in the creatinine output with the patient under standard conditions. They believe this to be a new contribu-

tion and consider it the expression of a fundamental disorder of muscle metabolism. They also demonstrated a striking difference in oxygen consumption between excised portions of paralyzed and nonparalyzed muscle. Chemical analysis of the muscle showed a low total inorganic phosphate, low creatinine and very low organic acid-soluble phosphorus.

KUBITSCHEK, St. Louis.

TACTILE IMAGINATION AND TACTILE AFTER-EFFECTS. WALTER BROMBERG and PAUL SCHILDER, J. Nerv. & Ment. Dis. **76**:1 (July) 1932.

This study is to some extent a sequel of the work on optic images previously published by Kanner and Schilder. Eight normal subjects, all physicians, together with a blind Negro who had recovered from a hallucinatory state, a boy of 13 in a hypnotic state and a patient with alcoholic delirium constituted the material. In none of the studies could tactual imagination be obtained without an optic imagination preceding it. Except in the blind, tactual impressions seemed to need the optic picture in order to make possible the correct spatial relationship of the object. Optic images of objects approaching the skin and images of lines thrown on the skin preceded the imagination of skin sensations. There was no correspondence between the optic pictures and the optic imaginations. Experiments showed that the areas of skin might be varied without any significant difference in the sensation. Vestibular irritation in the Bárány chair showed that the spontaneous tendency to motility in tactile imagination and the tendency to change in shape increase. The spreading of the touch and the rhythmic diffusion occurred as after-effects of a single touch. It was noted that imagination interfered with and provoked the tactual sensations again and again. In general, during the turning in the chair there is a tendency for tactile sensations to go in the direction opposite to that of the turning, and after stopping the tendency is in the direction of the turning. A distinct tendency toward curving of lines is noted as well as a difficulty in imagining angles and crossing points of lines. Slight touches have distinct after-effects of rhythmic character, lasting roughly up to three minutes. The author concludes that the multiplication tendencies play a less important part in tactual than in optic imagination and that the movements have a slower character in the former. Tactual imagination, unlike optic imagination, has strong subjective character and may even bear the quality of a sensation. Stein and Weizsäcker have described an increased liability of the threshold in lesions of the spinal cord, and the possible importance of the findings cited with such pathologic states is discussed.

HART, Greenwich, Conn.

DIAGNOSTIC INTEREST OF REFERRED PAINS IN THE TERRITORY OF THE CRANIAL NERVES. J. TERRACOL, Rev. d'oto-neuro-opht. **10**:246 (April) 1932.

The etiologic diagnosis of a headache is always difficult. It is important not to be deceived as to its origin in certain cases of referred pain. Well known examples, such as pain in the face during dressings in lateral sinus thrombosis, pain in the back of the neck in tonsillitis, ocular pain in acute otitis media and otalgia from lesions in the aerodigestive crossway, are mentioned. One explanation is the anastomotic relations between nerves, such as the inferior maxillary and Jacobson's nerve, the pneumogastric and Jacobson's nerve, and the recurrent meningeal of Arnold. The explanation is not always so simple. Painful impressions in the cranial region are transmitted to the neuraxis by the sensory roots of four cranial nerves—the trigeminal, the intermediary of Wrisberg, the glossopharyngeal and the pneumogastric. These nerves resemble spinal nerves in that they have ganglia, analogous to the spinal ganglia. Impressions brought from the periphery are conveyed from the ganglion cells to the gray nuclei in the bulb and pons. These are in close relation to one another. These nuclei are analogous to the nuclei of Goll and Burdach in the cord. The medullary dolorific fibers and those from the territories of the fifth, ninth and tenth pairs both reach the thalamus after synapses in the sensory nuclei. All the sensory pathways from the spinal, cranial and sympathetic systems meet in the thalamus. The rôle of the sympathetic (periarterial plexus) is considerable in these referred pains, especially

at the level of the cranial nerves. Furthermore, there is a mixture of the elements of the sympathetic system in each nerve trunk. Aubriot saw a case in which dressings of the mastoid wound caused violent pains in the arm and an eruption on the chest. Mahu operated on a man with bilateral nasal obstruction in two sittings; following each operation there was a zosterian eruption on the chest. It seems that the mechanism of referred pains in the territory of the cranial nerves and of the projection of visceral algias is identical. In the presence of a pain whose source cannot be proved to be local, it is important to think of a projected algia.

DENNIS, Colorado Springs, Colo.

CONTRIBUTION TO THE SEMEIOLOGY AND HISTOPATHOLOGY OF PELLAGRA WITH PARTICULAR CONSIDERATION OF THE EXTRAPYRAMIDAL SYSTEM. S. SZARVAS, A. STIEF and M. DANCZ, Schweiz. Arch. f. Neurol. u. Psychiat. **28**:139, 1931.

Although of late years pellagra has become less frequent in countries in which it had long been endemic, cases of the malady are being reported in increasing numbers from territories formerly spared. Since 1923, thirty-one cases have been reported from Hungary, all in inhabitants of the Tisza valley. Aside from the usual signs and symptoms of pellagra, well developed parkinsonism was the outstanding clinical feature in the first case reported in the present contribution. The patient, a man, aged 45, was mentally depressed and subject to delusions of persecution and extreme humility. When not in a state of delirium, he was well oriented and intelligent. The chief histologic changes, so far as the central nervous system was concerned, consisted in swelling and hyalinization of the giant cells of Betz, the large cells of the third layer of the frontal cortex and the anterior horn cells of the spinal cord, as well as extensive changes in the pallidum and vegetative nuclei of the floor of the third ventricle. Considerable depigmentation was noted in the substantia nigra, and hyaline changes were found in the walls of the small arteries of the cord. The authors express the view that the cachexia, trophic changes in the skin and severe diarrhea encountered in cases of pellagra are attributable to involvement of the vegetative nuclei. The second patient, a man, aged 51, was in a catatonic state on admission, the psychosis being regarded as an example of Bonhoeffer's reactive type. He later passed into a state of delirium interrupted by frequent lucid intervals. Like the first patient, he was greatly emaciated and presented the characteristic symptoms and signs of pellagra. Some of the other cases of pellagra studied by the authors showed signs of parkinsonism. All belonged to the poorest class of Hungarians, lived under bad hygienic conditions and subsisted, as a rule, on an exclusively carbohydrate diet, although none had eaten maize. The etiology of pellagra is discussed briefly.

DANIELS, Rochester, Minn.

TREATMENT OF CLONIC FACIAL SPASM: BY ALCOHOL INJECTION; BY NERVE ANASTOMOSIS. WILFRED HARRIS, Lancet **1**:657 (March 26) 1932.

True clonic facial spasm is a unilateral, intermittent or clonic series of contractions of the facial muscles, limited to one side, though not affecting the entire facial musculature to an equal degree. When the condition has developed, spontaneous cure of clonic facial spasm is unknown. The onset of the spasm varies in severity and frequency. On some days the patient may be comparatively free, while at other times the annoyance is excessive, aggravation frequently being induced by nervousness or excitement. During sleep the spasms always cease. Usually these commence in the orbicularis oculi, causing blepharospasm. The muscular contractions gradually spread to other facial muscles on the same side, especially those around the angle of the mouth, and ultimately every muscle supplied by the facial nerve of one side may share in the clonic contractions, including the frontalis and platysma and even the stapedius.

Pathologic findings in clonic facial spasm are unknown. It is probably due to some form of degenerative neuritis in the neighborhood of the geniculate ganglion, for in cases of several years' duration, it is always possible to demonstrate weakness of the facial nerve, contracture or overaction on that side.

Therapy in this form of facial spasm has been unsatisfactory. The author suggests anastomosis between the facial and the hypoglossal nerve as the only lasting treatment. It is too much to hope that the complicated and delicate movements of facial expression can ever be entirely reproduced, but the hypoglossal is a very active nerve so that, at least, good tonus is given to the musculature. Five patients were operated on; in each the spasm ceased. Facial movement returned to some degree in two patients after sufficient time had elapsed for the healing process. The other cases are too recent for motor recovery to have been produced at the time of this report. The operation is described in detail. Much space is given to data regarding after-treatment, which, according to the author, is second in importance to the operation itself.

BECK, Buffalo.

ETHNOGRAPHY OF SCHIZOPHRENIA. CUNHA LOPES, Arq. bras. de neuriat. e psiquiat. **15**:224 (Aug.-Sept.) 1932.

Lopes reviews the attempts at ethnographic classification of the human race from the times of Herodotus and Hippocrates to the present day, and states that they are without value because at present there are no pure races but only groups of persons possessing differentiated hereditary characteristics subject to slow but constant modifications. From the point of view of disease forms and races, which he divides into white, halfbreed and Negro, he studies a group of 147 native Brazilian schizophrenic patients, taken from the total material (970 patients) of the psychiatric clinic of the University of Rio de Janeiro. His tabulation shows that: (1) the Negro is subject to hebephrenia (53 per cent) although offering the lowest incidence of schizophrenia (17 per cent); (2) the halfbreed is more subject to paranoia (20 per cent) and offers a higher incidence of schizophrenia (26 per cent), and (3) the white race tops the list in general incidence of schizophrenia with a percentage of 55. It also shows that catatonia is less frequent in the halfbreed and the Negro, and that hebephrenia is more prevalent in the three races. The white race in Brazil is recruited from all the different peoples of Europe; the Negro race comes from the coast regions of Africa, especially from Portuguese Africa, and is being steadily assimilated, thanks to the lack of racial prejudice in the country. The aborigines constitute only a negligible factor and exhibit the cyclothymic rather than the schizothymic type. The author concludes that schizophrenia accounts for 15 per cent of the hospitalized patients, in the proportion of 2.04 per cent heboidophrenic, 50.34 per cent hebephrenic, 34.7 per cent catatonic and 12.9 per cent paranoid patients. He has accepted in his tabulation native Brazillians only, and he states that the psychiatric clinic attends to patients of every rank of society. This work will serve as a basis for future investigations on the incidence of clinical forms of schizophrenia in relation to ethnographic types, and on the evolution of schizophrenia among tropical inhabitants.

EDITOR'S ABSTRACT.

THE DIFFERENTIATION OF BEHAVIOR PATTERNS IN THE FOETUS AND INFANT. ORTHELLO R. LANGWORTHY, Brain **55**:265 (June) 1932.

The work of Coghill on Amblystoma punctatum is reviewed, and its fundamental characteristic, that the first reflexes represent the total activity of the organism, is emphasized. From a somewhat similar point of view the author studied several young opossums, 7 days old and 27 mm. in length, which were removed from the mother's pouch. The first contractions of the musculature of the opossum involve the trunk and the abdominal musculature and are very diffuse, enabling the animal to reach the pouch. Minkowski emphasized the diffuseness of early motor responses in the human fetus of from 2 to 6 months. Refinement

and delicacy of activity evolve later as differentiation from the response of the organism as a whole. With inhibition comes the more specific limitation of responses. Both Coghill and the author found in the amblystoma and the opossum, respectively, that activity in the spinal cord first develops in the cervical portion and progresses caudad; in the brain it begins in the medulla and progresses cephalad. Reflex patterns are always subservient to the total activity pattern in the opossum. This same phenomenon was also described in the human fetus by Minkowski. The development of early specific reflexes can be understood by Bok's hypothesis of the circle reflex. A sensory stimulus calls forth a diffuse motor response which in turn gives rise to stimulation of the proprioceptive endings in the muscle itself; Minkowski divides the development of control over segmental reflexes into the first stage, the embryonic or transition stage, in which the reflex is as yet inconstant and labile; the second stage, the early fetal or spinal stage, and the third stage, the tegmentospinal stage (the plantar reflex has the dorsal type of response). The final stage is the corticospinal. In the differentiation of the nervous system, tonic and postural reflexes appear very early. It is concluded that the mechanism of differentiation of all behavior patterns does not differ from that effective in the production of the conditioned reflex.

MICHAELS, Boston.

PARALYSIS OF THE LEFT SUPERIOR OBLIQUE WITH ANESTHESIA OF SYRINGOMYELIC TYPE OF THE RIGHT ARM AND THORAX AFTER CRANIAL TRAUMATISM. J. EUZIÈRE, H. VIALLEFONT and J. VIDAL, Rev. d'oto-neuro-opht. **10**:684 (Nov.) 1932.

A woman, aged 50, entered the clinic complaining of diplopia, stiffness of the right arm, disturbance of gait and lightning-like pains in the right hemithorax and arm when she sneezed. There was nothing significant in the family and previous histories except that thirty months previously an automobile accident had been followed by ecchymosis of the left eye. The injury was thought to be trivial. Since then, burns and cuts on the right side were not perceived. Detailed examination revealed scoliosis, paralysis of the left superior oblique muscle, anesthesia of syringomyelic type of the right arm and hemithorax, disturbances of equilibrium (dextropulsion and retropulsion) and pain of radicular type in the anesthetic area. Roentgenography revealed vertebral arthritis. The results of laboratory examinations were negative.

It is supposed that in this patient, who previously had vertebral rheumatism, the trauma had produced a minimal vascular lesion of the left cerebral peduncle in the peripheral and external part of the tegmentum. At this point the sensory tract for temperature and pain is near the border, and just behind it is the secondary acoustic pathway. The pathway for tactile sense is farther forward and more central. The sixth nerve winds around the peduncle at the same place. Hemorrhage from one of the small arteries in the neighborhood could account for the sensory syringomyelic hemiplegia and the paralysis of the patheticus. The proximity of the acoustic pathway explains the troubles of equilibrium, although these disturbances are frequent in cases of cerebral concussion and in this case were perphaps influenced also by the posterior cervical sympathetic syndrome that was present.

DENNIS, Colorado Springs, Colo.

PERIMETER SPOT-LIGHT OBJECT. JOHN N. EVANS, Arch. Ophth. **7**:614 (April) 1932.

The author has duplicated a Zeiss slit lamp bulb with an optical system that projects on the arc of the Ferree-Rand perimeter a round white spot of light graduated in different sizes, measuring on the arc 0.75, 1, 1.5, 2, 3, 4, 5 and 6 mm., respectively. The density of the light is adjusted by means of filters. The light is supported by a special iron bracket mounted beneath the light source of the Ferree-Rand perimeter. The author comments in his conclusions relative to the use of this apparatus for study of the form fields as follows: (1) Standard-

izable size, color and brightness of objects are obtained; (2) rapidity of taking of fields is increased; (3) scientific demands are adapted to clinical routine; (4) freedom from distortion is accomplished; (5) freedom from shadows and reflexes is secured; (6) colors and decreased illumination are accurately controlled; (7) neutral gray is a satisfactory arc color for white and colors; a black arc is also satisfactory; (8) it is practicable to adjust the brightness of the spot projected so that it compares accurately with the reflection factor of the usual paper disk objects, and (9) studies of the fields as made with the spot-light objects are identical in result with those mapped under parallel conditions, with the usual paper disk objects.

The disadvantages of the device may be cited as follows: (1) The original cost is large; (2) the device has a formidable appearance to the patient; (3) though the reflection factor is the same as that of the classic objects, and though the fields mapped with the spot-light object are identical in size and shape with those mapped with the white disks, there may be theoretical objections that they are not identical as stimuli.

SPAETH, Philadelphia.

TONIC PUPILS AND ABSENT TENDON REFLEXES: A BENIGN DISORDER SUI GENERIS; ITS COMPLETE AND INCOMPLETE FORMS. W. J. ADIE, Brain **45**:98 (March) 1932.

Adie suggests that most cases of "ophthalmoplegia interna unilaterale" are examples of tonic pupils and absent tendon reflexes in incomplete forms. The tonic pupil is usually unilateral and larger than its normal fellow, with the most important feature on convergence. The pupil dilates in the dark, and then contracts in diffuse daylight, sometimes to a size smaller than it was before. With more careful examinations, it is believed that true iridoplegia is rare. The Argyll Robertson pupil differs markedly from the tonic pupil, being unilateral in 5 per cent and small in 75 per cent in the author's experience; the tonic pupil is unilateral in 80 per cent and never small. Of nineteen of the author's patients with a tonic pupil, thirteen had abnormal reflexes. In the author's cases and those described by others, there were forty-five females and eighteen males. The age of onset has not yet been determined; however, the impression is that the abnormal pupillary reaction may appear at any age. Perhaps in a large majority of cases there may never be any symptoms. It is stated with some certainty that the tonic convergence reaction in pupils only apparently inactive to light is, in all probability, never a manifestation of syphilis of the nervous system. Delay, as well as slowness in responding, apparent inactivity to light, the regaining of a new size after the removal of the stimulus and slower relaxation, as compared with the rate of contraction to light, on convergence and, when present, in accommodation are the decisive diagnostic features of the tonic pupil reaction. Diphtheria, with its bilateral paralysis of accommodation, is distinct. With certain analogies to the myopathies, family periodic paralysis and the cataplectic attacks in narcolepsy, the nature of the disorder points to a disturbance of the vegetative nervous system.

MICHAELS, Boston.

THE RECOGNITION OF THE OPERATION OF CHANCE BY THE CHILD. MARGUERITE LOOSLI-USTERI, Arch. de psychol. **23**:45 (April) 1931.

In a continuation of her studies on the Rorschach test, the author has made some interesting observations on the capacity of the child to recognize the operation of chance as a causal phenomenon. Piaget has stated that this recognition does not exist in the child of 7 or 8 years, but the author finds such a capacity undeveloped in the child between the ages of 10 and 13 years. The absence of this capacity is associated with the absence of any attempt to interpret the Rorschach figures. Such an absence is not surprising, because the capacity to recognize the action of chance cannot exist until there is some recognition of the laws of cause and effect. In this the young child resembles the primitive. The recognition of the operation of chance as a causative factor occurs as the child begins to abandon his egocentricity—an important step in his development.

The resistance maintained by young children against the recognition of the possibility of chance as a causal phenomenon indicates that the child really desires not to acknowledge such a possibility because to recognize its existence is to acknowledge that reality may be different from fantasied reality, and thus to admit the possibility of doubt. It would seem that the recognition of the causal activity of chance occurs at the same time that the child is willing to entertain doubts as to the validity of the concepts he has accepted up to this time, and that both of these phenomena develop at the beginning of adolescence. Many, if not most, adults also show traces of resistance to this concept and oppose the destruction of their infantile world through occultism, mysticism, religion, etc. This article is extremely interesting and well worth reading in the original.

PEARSON, Philadelphia.

SPASTIC PSEUDOSCLEROSIS (CORTICO-PALLIDO-SPINAL DEGENERATION). CHARLES DAVISON, Brain **55**:247 (June) 1932.

Two patients, whose cases presented rather short, interesting clinical courses, had mental symptoms, pyramidal and extrapyramidal signs and muscular atrophy. Pathologically, the first case showed atrophy of the frontal cerebral convolutions, with destruction of the ganglion cells in the third, fifth and sixth layers, proliferation of the vessels, increase in the astrocytes of the cortical gray matter and of the white matter, destruction of the Betz cells and degeneration of the pyramidal tracts, demyelinization of the pallidal fibers and calcification of the pallidal vessels, and destruction of the nerve cells of the pallidum, corpus luysii and paraventricular nuclei and of the anterior horn cells. The second case, except for minor differences, presented a similar neuropathologic picture.

The literature is reviewed, especially the cases of the condition which Jakob designated spastic pseudosclerosis. The author's cases showed minor clinical differences, the absence of sensory disturbances and the absence of remissions; neuropathologically, there were no pronounced lesions of the thalamic nuclei, marked neuronophagia or glia rosettes in the present cases. It is considered that the calcification of the vessels in the globus pallidus was secondary to the pathologic process. The demyelinization of the white fibers of the globus pallidus resembles pathologically that described by Cécile and Oskar Vogt. The cases were closely related to Wilson's disease, pseudosclerosis of Westphal-Strümpell, chronic encephalitis and amyotrophic lateral sclerosis with mental symptoms, but sufficiently different so that the name "disseminated encephalomyelopathy" is suggested as being descriptive of its clinical and pathologic features; the author, however, believes that it is advisable to adopt Jakob's title, spastic pseudosclerosis.

MICHAELS, Boston.

THE CONDITIONED REFLEX OF THE CEREBRAL CORTEX. WILLIAM H. HICKS, J. M. Soc. New Jersey **29**:21 (Jan.) 1932.

The behavioristic doctrine can be traced from an a priori mechanistic philosophy established by Descartes in the seventeenth century, through an experimentally evidenced psychologic hypothesis propounded by Wundt in the nineteenth century and an enormously widened field of neuro-anatomy nad neurophysiology in the early twentieth century, to reach its direct exposition by Pavlov in 1906. With the conditioned reflex as the simple key, the door has opened to the explanation of the mechanism of behavior, and by that token, psychology has been elevated to the validity and dignity of a genuine science. Most behavior can be reduced to a reaction of gratification, of attention or of fear. These in turn can be analyzed into direct or conditioned reflexes of varying elaborateness. Carrying the study from the laboratory to the bedside, one can compare confusional states resulting from clashing stimuli with neurotic and psychotic behavior patterns. Variations in the stability of cortical reflex set-up may be translated into oddities of daily life, and hysteria can be explained on a purely mechanistic basis, without resorting to the mystic vagaries of the freudian

hypothesis. Successful treatment in cases of hysteria and neurasthenia is contingent on successful modification of the battery of stimuli—in a word, on environmental changes. The endocrine apparatus and the sympathetic nervous system constitute important controlling factors, as yet little understood. Evolutionary progress will continue, for every person with 10,000,000,000 neurons at his call has indeed the potentialities of becoming master of his fate.

DAVIDSON, Newark, N. J.

RECKLINGHAUSEN'S DISEASE WITH PAPILLARY STASIS OF THE LEFT EYE IN A PATIENT WITH A WOUND OF THE RIGHT EYE. VILLARD, DEJEAN and VIALLEFONT, Rev. d'oto-neuro-opht. **10**:690 (Nov.) 1932.

A patient, aged 20, was wounded in the right eye by the explosion of a detonator. A traumatic cataract resulted. It was removed a few weeks later. Examination of the right eye revealed a secondary cataract and two white areas of retinal exudate; vision was reduced to 1/10 with correction. In the left eye, papillary stasis was observed; vision was 8/10. Neurologic examination revealed an infantile aspect, with no psychic disturbance, uncertainty of gait, slight adiadokokinesis and dysmetria, deviation of the extended arms, intracranial hypertension and pigmented spots and tumors on the chest and the back. There was no change in the genital organs, and laboratory examinations gave negative results. The right labyrinth was hypersensitive. Roentgenograms revealed deepening of the floor of the sella turcica and erosion of the clinoid processes. The diagnosis was intracranial localization of tumors of Recklinghausen's disease in the sella and the eighth nerve. The papillary stasis was attributed to intracranial hypertension because sympathetic ophthalmia is rarely manifested except by optic neuritis; the sympathizing eye was not painful; the optic neuritis was not inflammatory, but rather of the type of stasis with tumefaction, and there was good visual acuity. From a medicolegal point of view the right eye is practically lost, with disability of 30 per cent. The papillary stasis is probably of recent date and is not the result of the accident. The visual and general prognosis is poor. No efficacious therapy for Recklinghausen's disease is known.

DENNIS, Colorado Springs, Colo.

EXPERIMENTAL DENTAL NEURITIS OF THE TRIGEMINUS. B. SPITZER, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **34**:83, 1932.

Spitzer, using aseptic precautions, exposed the pulp cavities of the canine and first molar teeth on one side of the lower jaw in three anesthetized dogs. He injected a freshly boiled 5 per cent solution of macerated jequirity into the pulp, by means of a very fine cannula. The quantity injected varied from 0.5 to 0.75 cc. The dogs were allowed to live eight, twenty-one and twenty-eight days respectively. None of the animals showed the slightest evidence of pain or other discomfort during the period of survival. After the animals were killed the normal mandibles as well as those into which the injections had been made were examined histologically. The gasserian ganglia were subjected to a similar examination. The pulp of the affected side revealed an inflammatory process which extended to the nerves, although the central portion remained unaffected. The mandibular nerve disclosed definite inflammatory foci along the longitudinal axis of the sheath, and in some places the inflammation seemed to have invaded the nerve itself. In other words, there were definite perineuritis and endoneuritis. Foci of inflammation were also observed in the gasserian ganglion on the affected side. There was only a slight reaction in the roots of the nerves. It is noteworthy that a similar process was found in all the animals, and that four weeks after the injection was made the lesions in the gasserian ganglion were still florid. As it is difficult to conceive that the pulp itself was infected and that a latent virus within was activated which caused the inflammation, it must be assumed that a simple toxin may have an effect on living tissues similar to that of a living virus.

KESCHNER, New York.

STUDIES OF THE PATHOGENESIS OF MULTIPLE SCLEROSIS: III. FURTHER EVIDENCE OF ABNORMAL LIPOLYTIC ACTIVITY IN THE BLOOD IN MULTIPLE SCLEROSIS. RICHARD M. BRICKNER, Bull. Neurol. Inst., New York **2**:119 (March) 1932.

In previous studies the author found (*a*) that the myelin in rats' spinal cord, after immersion in plasma of persons with multiple sclerosis, showed greater degeneration than after immersion in normal plasma and (*b*) that serums from multiple sclerosis incubated with a lecithin emulsion produced a hydrolyzing action on the lecithin which differed definitely from that produced by the use of serums from normal persons and persons with other diseases. The author is of the opinion that the myelinolytic agent in the blood in multiple sclerosis may be lipolytic or liposic. The present study reports the results of a third test of this hypothesis, the hydrolyzing effect of serum in multiple sclerosis and nonmultiple sclerosis on different esters—an adaptation of Falk's method. Patients with multiple sclerosis were tested and as controls the blood of fifty-two normal students and thirty-eight patients with diseases other than multiple sclerosis, most of which were of the nervous system, was used. The technic and the results are given in detail, and the results indicate that there is a striking difference in the lipolytic, and probably liposic, activity of multiple sclerosis serum from that of the control serums. It is frankly admitted that the cause of the abnormal lipolytic activity in multiple sclerosis is unknown. Its pathogenicity is considered still hypothetic but probable. The experiments with modifications are being continued with the aim of making individual tests possible.

KUBITSCHEK, St. Louis.

CONTRIBUTION TO THE CLINICAL AND ANATOMIC STUDY OF THE MNEMIC FUNCTION: THE AMNESIC SYNDROME IN A CASE OF GLIOMA OF THE CORPUS CALLOSUM. G. DE MORSIER, Schweiz. Arch. f. Neurol. u. Psychiat. **28**:283, 1932.

Morsier presents evidence in support of the view that the "acquisivité mnésique," disturbance of which constitutes the essential feature of Korsakoff's amnesia, is a function of the prefrontal lobes. After a brief historical survey, the author enumerates the various conditions in which a fixation amnesia has been encountered. Although in general cases with a generalized increase in intracranial tension had to be excluded from the present study, a deficiency of the "acqusitivité mnésique" was found to be a symptom not only in all reported cases of tumor but also in degenerative and inflammatory conditions involving both prefrontal lobes. Further support for the author's thesis seemed to be furnished by the results of ablation experiments. In lesions confined to the one frontal lobe, on the other hand, amnesia was found to be a variable symptom. The fact that the ability to recall events of the past may remain unimpaired with disease of the frontal lobes prompted the belief that certain paths of vital importance to the mnemic function connect these centers with the posterior portions of the cortex. That these paths cross to the opposite hemisphere in the posterior portion of the corpus callosum was indicated by several observations of a fixation amnesia in lesions involving the splenium. The author suggests that in Korsakoff's psychosis, the toxin possesses an affinity for these tracts, giving rise to "a form of occipitofrontal neuritis." A case of glioma of the splenium of the corpus callosum is reported with illustrations.

DANIELS, Rochester, Minn.

MÜLLER'S REACTION IN THE CEREBROSPINAL FLUID. N. SACCHETTI, Riv. di pat. nerv. **40**:94 (July-Aug.) 1932.

Sacchetti reports his experience with Müller's reaction in 194 cerebrospinal fluids. The reaction is one of flocculation and requires the use of an antigen, which is prepared by Sherring. The antigen is diluted with a physiologic solution of sodium chloride and left to mature in an oven at 17 C. The matured antigen is dissolved in 25 cc. of solution in a glass tube, 50 mm. in diameter. According to

Müller, the caliber of the tubes and the temperature of the solution are important factors in the reactions. The solution is then distributed in several test tubes to which 0.6 cc. of cerebrospinal fluid, previously inactivated, is added. The reading must be made three or four hours later; a solution that presents a distinct conglutination after this time is considered distinctly positive (++). Fluids which after three or four hours do not show definite conglutination, but only flakes, and in which conglutination appears on the following day are called slightly positive, and those that show flakes only on the day after are considered as doubtful.

From results with 73 syphilitic and 12% nonsyphilitic fluids, Sacchetti concludes that, in comparison with the Wassermann reaction, Müller's reaction in the cerebrospinal fluid has the advantage of a slightly higher sensitivity, and may be used to detect slight involvement of the meninges in cases in which the Wassermann reaction is negative. This applies particularly to the cerebrospinal fluid of patients with dementia paralytica who have been treated with malaria, in which Müller's reaction seems to improve following improvement in the Wassermann reaction.

FERRARO, New York.

PSYCHOSES ASSOCIATED WITH MALARIA. N. SKLIAR and M. RJABOWA, Monatschr. f. Psychiat. u. Neurol. **78**:1 (Jan.) 1931.

A clinical analysis is made of seventy-five cases of malaria in which psychoses occurred. There were seven cases of dementia praecox in the group, six of manic-depressive psychosis, seven of dementia paralytica and seven of hysteria. In them the malaria was regarded merely as a precipitating factor. Skliar and Rjabowa devote most of their attention to the remaining cases, in which various exogenous types of reaction were observed. A large number of the patients had exhibited psychopathic traits previous to the malaria. The authors are of the opinion that different exogenous factors are apt to lead to transitory mental disorders in psychopathic persons. However, they are unable to confirm Kleist's view that certain persons are particularly predisposed to infectious psychoses. The patient with malarial psychoses showed an unusually high proportion of twilight states (56.3 per cent) and a small proportion of simple fever deliria (12.5 per cent). In the majority of the cases the psychosis occurred fairly early in the course of the disease. There were only two cases of amentia and one of post-infectious delirium. In most instances the mental make-up was reflected in the symptoms. Four patients showed short recurrent psychotic episodes that replaced the paroxysmal rises of temperature. They were characterized by motor restlessness and anxiety, with dysesthesias, noises in the ears, sweating and a marked feeling of discomfort. This type of clinical picture was the only one that might be regarded as specific for malaria.

ROTHSCHILD, Foxborough, Mass.

MALIGNANT HYPERTENSION SIMULATING BRAIN TUMOR. O. H. PERRY PEPPER, Pennsylvania M. J. **35**:75 (Nov.) 1931.

Malignant hypertension in children frequently affords a clinical picture closely resembling that of tumor of the brain. In both instances the patient is likely to suffer from headache, vertigo, projectile vomiting, convulsions, impairment of vision and perhaps transient aphasia. In both instances examination may show papilledema, increased spinal fluid pressure and localizing cerebral symptoms. The latter findings result from scattered areas of softening within the brain. Points of differentiation between the two diseases are: 1. The headache, intense and progressive in both conditions, in malignant hypertension is more likely to be localized in neoplasm and more apt to be throbbing. 2. The papilledema may be equally severe in either case, but the experienced ophthalmoscopist will find hyperemia of the disk and sclerosis of the retinal arterioles as well as other evidences of degeneration of the retina in cases of hypertension. 3. The blood pressure is seldom elevated in cerebral neoplasm, except in instances of sudden increase in intracranial pressure, whereas it is characteristically high in the

former disorder. 4. Evidences of renal damage frequently appear in the later stages of malignant hypertension. The differentiation of the two diseases is essential because they require different kinds of therapy. Decompression is probably never justified in cases of malignant hypertension.

DAVIDSON, Newark, N. J.

POSTURAL AND VEGETATIVE TONUS, IN POSTENCEPHALITIC SYNDROMES, AND ITS MODIFICATION WITH HORIZONTAL VIBRATORY STIMULATION. G. B. CACCIAPUOTI, Ann. di neurol. **45**:81 (May-June) 1931.

There exists a parallelism between the postural tonus and the vegetative phenomena in chronic encephalitic syndromes. The common syndrome in flexion is thus accompanied by a sad expression and vagotonia, with exaggeration of the Dagnini-Aschner (oculocardiac) reflex, while the syndrome in extension is accompanied by an hilarious expression and sympatheticotonus, with either abolition or inversion of the Dagnini-Aschner reflex. It is interesting to note that scopolamine and related drugs usually accentuate the symptoms of patients in extension, while they attenuate the symptoms of patients in flexion.

Using a vibration apparatus at a frequency of from 4 to 8 vibrations a second and applied horizontally to the upper part of the back between the scapulae, the author obtained amelioration of the symptoms in patients suffering with the flexion syndrome. It was noted that immediately after the institution of the treatment the body and limbs became erect, and the facial expression changed from one of sadness to one approaching normal. The effects of the treatment last for about an hour. When the vibration is applied anteriorly and to patients suffering with the syndrome in extension, a marked reduction of the extension of the torso and limbs and an amelioration of the facial expression occurs.

IMPASTATO, New York.

VAGUE PAINS OF NEURASTHENIC PATIENTS. P. OLINTO, Arq. bras. de neuriat. e psiquiat. **15**:231 (Aug.-Sept.) 1932.

Olinto states that the pains of neurasthenia are of uncertain localization, inconstant, transitory and aggravated by having attention focused on them. They are not always due to autosuggestion but may be produced by exaggerated emotivity. Mental reactions are muscular, glandular or cerebral and may originate in stimulations of the corresponding medium or proceed from mental images. The motor force of these images proves this statement, as any movement thought of is exteriorized, and emotions and mental images determine actions and inhibitions. The muscles contract or expand according to temperaments. Cycloid and schizoid muscular reactions are well differentiated, and nervous exhaustion often attacks their respective constitutions. When the chronaxia of the motor nerve does not correspond to that of the muscle or when between two synapses a third inhibitory one intervenes, there is an impediment in the nerve conduction; a fixed idea may interfere with the free course of the stimuli and prevent the usual response to them. If muscles are immobilized for some time they become tired, lactic acid is produced in their tissue, and pain is present. These pains are delayed and difficult to account for by the patient and in the clinic. They do not respond to analgesics, and, being a result of some mental disturbance, they cease only when the mental disturbance disappears.

EDITOR'S ABSTRACT.

CAN BIRTH CONTROL REDUCE INSANITY? H. A. COTTON, Birth Control Rev. **16**:12 (Jan.) 1932.

Five hundred cases of so-called functional types of mental disorders were analyzed by the author in relation to the order of birth. The following startling facts were deduced from the tabulation of the data. "Cases in which the patient was the only child amounted to only 19, while the first child was found to be

insane in only 65 cases. Thus only 5 per cent of the number were only children and only 23 per cent of this group including the only child were the first children. In other words, 77 per cent of the cases occurred in children who were born after the first child." Relying on such data as this, Dr. Cotton later states: "In view of these facts it appears to me that if we cannot make any inroads on the increasing ratio of insanity by other methods, that birth control offers a very sure method of decreasing the number of insane patients admitted to the institutions." A glance at the amateurish statistical methods used in this paper shows that there are numerous obvious fallacies. In the opinion of the reviewer the number of cases used is not large enough, nor uniform enough to allow of statistical treatment. The table really proves nothing and certainly does not justify the conclusions quoted. Such misleading deductions published in a magazine the object of which is obviously propaganda does harm to the cause of psychiatry.

COBB, Boston.

EXPERIMENTAL DETERMINATION OF SEX. SCHÖNER, Fortschr. d. Med. **49**:835 (Oct. 30) 1931.

The author claims to have offered, in 1909, the theory that from the right ovary twice as many males are derived as females, and from the left ovary twice as many females as males. He collected in Berlin 142 cases of unilateral ovariotomies and found 43 boys and 27 girls derived from the right ovary; while from the left ovary there were derived 49 girls and 28 boys. With the addition of 123 cases of cesarean section, the percentage from the right ovary was 62 per cent boys and 37 per cent girls, and from the left ovary 56 per cent girls and 43 per cent boys. The author states that the location of the corpus luteum was made in 1,105 cases; in those cases in which the corpus luteum was situated in the right ovary 368 boys, or 63 per cent, and 209 girls, or 36 per cent, were produced; in those cases in which the corpus luteum was located in the left ovary 337 girls, or 64 per cent, and 191 boys, or 36 per cent, were produced. As additional proof of his theory, the author investigated 14,466 twin births. According to the author's theory, there should be twice as many twins of the same sex as of the opposite sex. He found 4,727 boy twins and 4,550 girl twins, or altogether, 9,277 twins, 64 per cent, of the same sex, and 5,189 twins, or 36 per cent, of different sex.

HART, Greenwich, Conn.

PATHOLOGIC ANESTHESIA OF THE CORNEA. L. CERISE and R. THUREL, Ann. d'ocul. **169**:142 (Feb.) 1932.

In the first section of the article, the different methods of examining corneal sensitivity are considered and the insufficiency of the methods employed generally in clinics is stressed. The authors suggest the use of a special apparatus to study corneal sensitivity by the aid of the hairs of *blaireau étalonnes* weighing from 200 to 250 mg. After studying normal corneas they investigated keratitis with anesthesia, also secondary keratitis with corneal anesthesia and particularly neuroparalytic keratitis. The end of the report is devoted to the study of sensitivity of the cornea and corneal reflexes in pathologic conditions of the nervous system: (1) the modifications in trigeminal involvement, and (2) in lesions of the central nervous system. In the first group, Cerise and Thurel stress the great importance of the reduction of corneal sensitivity as an early sign of involvement of the fifth nerve, often preceding the appearance of pains, and the diagnostic importance of corneal anesthesia in facial neuralgia. Corneal anesthesia of central origin should be differentiated from anesthesia due to peripheral lesions. The authors stress the fact that corneal anesthesia is frequently found in tumors of the region of Rolando but is rare in tumors of the cerebellum.

BERENS, New York.

POLYNEURITIS: AN EPIDEMIC OF PECULIAR ORIGIN. J. W. TERBRAAK, Nederl. tijdschr. v. geneesk. **75**:2329 (May 2) 1931.

Ten cases of polyneuritis in pregnant women, in which the symptoms were, essentially, symmetrical paralysis of distal muscle groups without any objective disturbance of sensibility, are described by the author. Patellar reflexes were retained, but the achilles jerks were absent. In nine of the cases a cathartic of dark color had been consumed from ten to twenty days previously. Electrical testing of the muscles showed partial and total degeneration of the small muscles of the hands and feet. Early and strikingly affected was the opponens pollicis. At the onset of the illness, the patients complained of vomiting, diarrhea and abdominal pain. One woman had an abortion. Two or three weeks after the appearance of the muscular symptoms, paresthesias and paresis developed in the feet and later in the hands. A reducing substance was found in the urine. The atrophy was not pronounced. The loss of electrical response suggested a prolonged recovery. One of the women had used a French cathartic called "apiol," which contained phenolates and an ethereal extract of petersilien seeds. The poisonous nature of this material is well known. Whether the extract of petersilien alone or the mixture of the ingredients in the cathartic was responsible remains unsettled.

HART, Greenwich, Conn.

THE RELATION OF BIRTH TRAUMA TO NEONATAL MORTALITY AND INFANT MORBIDITY. HUGO EHRENFEST, Am. J. Dis. Child. **43**:426 (Feb.) 1932.

This report, which was read at the White House Conference for Child Health and Protection, details no new facts concerning birth trauma but is essentially an appeal for more careful clinical and postmortem examinations in the cases of infants who die at or about the time of birth. The author reports in general a large series of autopsies done on stillborn infants and those dying within the first few days of life, in which fatal lesions within the cranium were discovered in about 25 per cent of the cases; another 25 per cent showed cerebral damage, which need not have been fatal. In about 50 per cent of the autopsies a hemorrhage into the suprarenal glands was noted. Attention is also directed to the frequent occurrence of injuries of the spinal column and cord, rupture of the liver and other physical accidents that led to death within a few days of birth. He states that many physical abnormalities noticed early in life are frequently interpreted as congenital, while as a matter of fact they may be the consequences of injury sustained at birth. The possible etiologic relation of nonfatal intracranial damage to mental deficiency is also touched on. This article is by nature more of a preface than a contribution to knowledge of birth trauma.

LEAVITT, Philadelphia.

REGENERATION IN NEMERTEANS: III. REGENERATION IN LINEUS PICTIFRONS. W. R. COE, J. Exper. Zool. **61**:29 (Jan. 5) 1932.

In the Pacific nemertean Lineus pictifrons the capacity for complete regeneration and regulation extends from the anterior end of the lateral nerve cords to the middle of the foregut. Anterior to the nerve cords only anterior regeneration occurs, while posterior to the middle of the esophageal region only posterior regeneration is usual. Complete regeneration and individualization occur only in the presence of a portion of at least one of the lateral nerve cords; hence the organizing potency for such regeneration is thought to be situated in these nerve cords. Anteriorly the line of demarcation between complete and incomplete regeneration is sharp, being identical with the anterior end of the nerve cords, but posteriorly the percentage of complete regenerations gradually diminishes and is greater in young and in small regenerated than in mature worms. The extent of this controlling factor, which induces complete individualization in this species, is thus intermediate between that of most heteronemertea, where the so-called organization center is limited to the anterior end of the nerve cord, and that of other species, where it extends the entire length of the cord.

WYMAN, Boston.

INNERVATION OF RED AND WHITE MUSCLE. CHONG RYUN RI, Keijo J. Med. **2**:585 (Dec. 31) 1931.

Nakanishi and Hayashida have stated that in the tetanic contraction of the red muscles of the extensors in the cat there is an inhibitory mechanism at work through which the contraction is made possible. Until now, knowledge of the physiologic significance of the red muscle fiber has been slight. It is known that the red muscles contract more slowly and have a longer latent period than the white, and that the motor nerve fibers of the soleus muscle have a higher threshold to stimuli than those of the gastrocnemius. The author undertook experiments with decerebrated cats; the aforementioned muscles were isolated, and he found that the contraction of the soleus muscle was more lasting and had a longer latent period than that of the gastrocnemius. He found, after the cutting of the spinal motor nerve roots supplying these muscles, that the excitability of the soleus was much greater than that of the gastrocnemius. He believes that the former is innervated to a higher degree than the latter, and that in the extensor muscles of the cat's extremities the nerve branches to the red muscles have a greater percentage of small myelinated fibers than those to muscles consisting of both red and white muscle fibers.

HART, Greenwich, Conn.

INITIAL INSPIRATION IN THE MAMMALIAN FETUS. E. L. COREY, J. Exper. Zool. **61**:1 (Jan. 5) 1932.

The fetus of the albino rat is first capable of spontaneous respiratory movements at approximately 18 mm. of crown-rump length. Ligation of the umbilical cord initiated respiratory movements under all conditions imposed on the fetus in the experiments. Under the influence of asphyxia, respiratory movements took place in utero, within the amniotic sac, in an isotonic solution of sodium chloride at body temperature, in air, and under a pressure of 200 mm. of mercury. Cooling is of little importance as a factor in the initiation of the first inspiration, since asphyxiated fetuses respired with equal facility at either room or body temperature. Drying of the skin may be responsible for initiating respiration without asphyxia. The initial inspiration of the mammalian fetus is brought about by the asphyxia coincident with the separation of the placenta from the uterus at birth. Drying of the skin on contact with the air may act as an accessory factor in the process, but it must be considered as a relatively weak one in the initiation of the first inspiration.

WYMAN, Boston.

CEREBELLAR APOPLEXY. JOSEPH C. MICHAEL, Am. J. M. Sc. **183**:687 (May) 1932.

There is a marked paucity of reports concerning apoplectiform cerebellar disease in the literature. The symptomatology presents three groups: (1) fulminating, without premonitory signs; (2) grave, with premonitory symptoms of severe occipital pain, sensation of turning and inability to stand up, nausea and vomiting, impairment of consciousness, cerebellar signs with the absence of pyramidal tract involvement and usually blood in the spinal fluid, and (3) benign, with less constant and less pronounced premonitory signs. In the majority of cases arteriosclerosis with hypertension is found and occasionally syphilitic arteritis; diabetes in young persons and birth trauma are other infrequent causes. The rare incidence (0.0058 in 17,257 cases) might be due to the liberal anastomosis of the blood vessels in the median of the vermis. The postmortem observations and clinical notes in ten cases are described; nine cases occurred in persons past the age of 42; in seven cases degeneration of the cerebral vessels was also found.

MICHAELS, Boston.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, March 16, 1933

PERCIVAL BAILEY, M.D., *President, Presiding*

PULSATING EXOPHTHALMOS DUE TO AN ARTERIOVENOUS VARIX. DR. HALE A. HAVEN.

The patient, a man, aged 38, was admitted to the neurosurgical service of the Michael Reese Hospital on Feb. 4, 1933. The past history is irrelevant, except that he was struck on the head with a brick in July, 1932, when he sustained a slight laceration of the scalp over the left occiput for which he did not seek medical care. He apparently recovered and was well until about three months before entering the hospital, when he first noticed a slight prominence and reddening of the scleral vessels of the left eye. Two months before entrance he began to hear pounding and whistling noises in the left ear. The noises seemed to come from the left frontal region and were most marked when he lay on the left side. Exertion made no difference in the volume of the sound, but lifting a weight or straining would make the left eye more prominent. Six weeks before entrance to the hospital he began to see double on looking to the left. The prominence of the eyeball seemed to be progressive.

There was pulsating exophthalmos of the left eye, the scleral vessels of which were markedly dilated. Exophthalmometric measurements were 35 mm. for the left eye and 28 mm. for the right. A bruit was heard over the eye, the left side of the forehead and the left temporal region; it was transmitted down the left carotid artery. The pupils were equal, and the movements of the extra-ocular muscles were performed well. It was thought that the diplopia was due not to weakness of a muscle but to loss of movement because of the marked exophthalmos. The fundi appeared normal, with retained deep central excavations and only slight engorgement of the veins of the eyes. It was questionable whether those in the left eye were more dilated than those in the right. The bruit could be stopped by pressure over the left carotid artery. A diagnosis of arteriovenous aneurysm was made.

The patient was fitted with a collar by means of which pressure could be maintained on the left carotid artery. At first it was worn for ten minutes every hour during the day and was left off at night. Within five days the time was gradually increased, to thirty minutes every two hours. At that time the exophthalmometric measurements were 22 mm. for the right eye and 28 mm. for the left. The vascular dilatations in the left sclera were then barely noticeable. The time of wearing the collar was increased gradually until the patient wore it comfortably for ninety minutes every two hours. On Feb. 27, 1933, an operation was performed by Dr. Loyal Davis. The left common carotid artery was ligated about 1 cm. below its bifurcation.

The patient made an uneventful recovery. There were no untoward neurologic manifestations, and the patient was discharged from the hospital as cured seven days after the operation. At that time no bruit could be heard at any place over the skull or along the course of the carotid artery. The left eye appeared to be about even with the right. The exophthalmometric measurements were 22 mm. for the right eye and 25 mm. for the left. No bruit has developed since, and it is our belief that the patient will remain well.

TUMOR OF THE MEDULLA OBLONGATA: REPORT OF A CASE. DR. BENJAMIN H. KESERT (by invitation).

A man, aged 40, was admitted to the Edward Hines, Jr., Hospital on Dec. 27, 1932, because of "sinusitis." The family and past histories are without significance. The patient became ill on Dec. 23, 1932, at about 3 a. m., when he suddenly began to vomit. He continued to vomit at intervals until about 8 a. m. He became so weak that he remained in bed; on December 26 he began to have difficulty in swallowing. Fluids returned through the nose. He also began to have difficulty in speech and complained of double vision, dizziness and severe frontal and occipital headaches.

The patient had had a similar attack, though it was not so severe, about the last week in September, when he remained home from work for almost two weeks. He had frontal headaches, double vision and numbness of the right side of the face at times. He was told by a physician that he had sinus trouble. When he returned to work, he had difficulty because of the headache, which continued until the time when he became ill again.

Physical examination at the time of admittance revealed a well nourished and well developed man who appeared to be acutely ill. The weight was 175 pounds (79.4 Kg.); the blood pressure, 130 systolic and 90 diastolic; the pulse rate, 96, and the respiratory rate, 20. The heart tones were distant but regular; otherwise, physical examination gave essentially negative results. There was crusting on the right inferior turbinates, and the basal septum deviated to the right. There was no evidence of maxillary sinusitis.

Neurologic examination revealed a tendency to fall to the right when the patient sat up in bed. There was no rigidity of the neck; the Kernig sign was not present. Percussion of the skull did not elicit pain in any area, nor was there a change in the tone of the sound produced. The pupils were equal and reacted to light and in accommodation; there was rotatory nystagmus, with the slow component to the right; there was diplopia on looking to the left; corneal anesthesia was present only on the right; the fundi were normal. There was no facial weakness. The tongue was protruded well in the midline. There were no atrophies. Swallowing was difficult, causing the patient to choke. Speech was indistinct and of a bulbar type. Power in all of the extremities was fairly good; however, the deep reflexes were weak bilaterally. The abdominal and cremasteric reflexes were present on both sides. No Babinski sign or other pathologic reflex was elicited. Sensibility to pain was impaired in the left leg.

Laboratory examinations of the blood showed: erythrocytes, 4,250,000; leukocytes, 9,800; hemoglobin, 80 per cent; on the following day a count revealed: leukocytes, 14,700; polymorphonuclears, 86 per cent; nonprotein nitrogen, 54; creatinine, 2; sugar, 117.6; the Wassermann and Kahn tests were negative. Examination of the spinal fluid showed no evidence of a block; the pressure was normal, and the appearance clear, with 16 cells; the Wassermann test was anticomplementary, and the Lange curve, 0012221100. Spinal puncture was repeated on the day of death, when there were 28 cells; the Wassermann test was again anticomplementary, and the Lange curve, 333222100.

The temperature at the time of admission was 99 F.; it rose to 104 F. before death. The heart became rapid; the pulse could not be felt at the wrists for two days before death. Hiccup was also noted. On December 30, the patient became more irrational and stuporous; on the morning of death, December 31, he was in coma. Breathing on that day was of the Cheyne-Stokes type. The skin was cyanotic and cold.

At autopsy, the essential pathologic changes were confined to the medulla. There were no adhesions to the dura. The longitudinal and transverse sinuses were clear. When the dura was removed, a slight excess of fluid was noted. Some edema of the meninges was seen, especially beneath the pia-arachnoid. All of the vessels of the brain were engorged. When the brain was removed, a small, grayish-pink area was observed in the medulla on the right side, which on section measured 0.5 by 1 cm.; it occupied the lateral funiculus, was not encapsulated and was soft.

At autopsy it was thought that the lesion was a tumor, but microscopic sections revealed an inflammatory lesion.

Microscopically, the pia-arachnoid was markedly thickened. In the medulla oblongata were numerous foci of recent hemorrhages, with well preserved red cells intermingled with many scavengers containing black pigment. Around the blood vessels there was marked cellular infiltration with polymorphonuclear and small mononuclear cells. The adventitia of these vessels was thickened, and the endothelium was swollen. In other areas the nerve tissue was edematous, forming sievelike areas which contained polymorphonuclear cells. There was no evident progressive glial reaction.

The microscopic diagnosis was: purulent encephalitis limited to the medulla oblongata, and recent hemorrhages into the medulla.

DISCUSSION

DR. PETER BASSOE: I saw the patient on the day before he died. The case impressed me as one of acute bulbar encephalitis of some kind affecting chiefly deglutition and speech. The case proves that a lesion in the medulla oblongata affecting the vagus or its roots may produce such symptoms. When I heard that a tumor had been found, I was surprised; however, a tumor may not produce marked changes until it touches the vagus; when it finally affects the vagus, it quickly produces symptoms which, as a rule, except in the rare, slowly growing tumors with which a picture of syringobulbia may be produced, are those of acute bulbar paralysis.

Of course, the differentiation between bulbar abscess and encephalitis is difficult. We are a little at sea as to the origin of the abscess. There was no general necropsy, and there may have been a chronic focus in the lungs or elsewhere that gave rise to a metastatic focus in the bulb. It would seem strange for a sinus infection to cause this type of lesion.

DR. A. B. YUDELSON: Will Dr. Kesert give the time that elapsed between the second lumbar puncture and death? What was the indication for the second lumbar puncture?

DR. BENJAMIN H. KESERT: On the day of the patient's death, at 8 a. m. he was becoming worse; as we had made a diagnosis of acute bulbar encephalitis, I suspected purulent spinal fluid. A spinal puncture was therefore performed. The patient died at about 10:30 a. m.

GALVANIC SKIN REFLEX AND REACTIONS OF THE BLOOD PRESSURE IN THE PSYCHONEUROSES. DR. ALFRED P. SOLOMON and DR. THOMAS L. FENTRESS.

Sixty-seven patients with an active psychoneurosis at the outpatient department of St. Luke's Hospital have been studied. The technic consisted in obtaining photographically continuous records of the galvanic skin reflex (Féré phenomenon) and of the reactions of the blood pressure to sensory, indifferent and crucial ideational stimuli. For convenience the cases were classified according to freudian terminology. It was found that patients with anxiety neuroses had low electrical resistances and low absolute, galvanic reactions in ohms. The cases of conversion hysteria showed a high electrical resistance and large, absolute galvanic reactions in ohms. In the anxiety hysterias, compulsion neuroses and mixed psychoneuroses, low resistance and low reactions were found whenever a large amount of free anxiety was present.

The hypothesis is presented that the total energy of a given person is the sum of the free energy or anxiety and the bound energy. Energy is considered to be bound by such psychoneurotic mechanisms as conversions and compulsions, or by normal activity. Free energy or anxiety is assumed to result in stimulation of the sympathetic system. The galvanic skin reflex has been taken as a convenient measure of the degree of sympathetic stimulation. The hypothesis is in agreement with the observations.

In conversion hysteria, a high electrical resistance is constant. In the presence of a hysterical attack without muscular movements, the size of the absolute, galvanic reactions was smaller than would be anticipated. An increased stability of the binding of energy is suggested as an explanation of this low reaction.

The reactions of the blood pressure, which were taken simultaneously, showed no significant findings except the increased size of the reactions in the cases of compulsion neuroses.

GALVANIC SKIN REFLEX AND REACTIONS OF THE BLOOD PRESSURE IN THE PSYCHOSES. DR. CHESTER DARROW (by invitation) and DR. ALFRED P. SOLOMON.

This article will be published in full later.

DISCUSSION OF PAPERS BY SOLOMON AND FENTRESS AND BY DARROW AND SOLOMON

DR. JOHN FAVILL: I confess that the large mass of data is too great for my immediate absorption, and that critical discussion is out of place. I have watched the work at St. Luke's Hospital for a year without participating, and I believe that many possibilities will develop when one takes time to digest and check up the findings. I wonder whether something interesting would be discovered if the test procedure were carried out at the moment of awakening from a catatonic stupor brought about suddenly by mixtures of carbon dioxide and oxygen.

DR. CLARENCE A. NEYMANN: Were the measurements made by potentiometer or by galvanometer? How was the pressure controlled? What was the size of the electrodes, and the amount of pressure on the skin? I have had difficulty in balancing the Wheatstone bridge with the galvanometer. With a potentiometer the procedure may be easier. All experiments of this nature are open to the criticism that the reaction of the skin is extremely variable.

DR. R. P. MACKAY: I wish to express my admiration for this attempt to chart out a field which is at present poorly understood. The psychologic approach to these problems has led to so much dissension and even vituperation that it is refreshing to witness an attempt to work them out from an objective and practical standpoint. The presentations this evening have been difficult to follow because of the complexity of the material, but they are undoubtedly of importance. I was particularly struck with the conception of bound energy as expressed by Dr. Fentress. He pointed out that patients with hysteria or obsession and compulsion neuroses often present a high skin resistance combined with a minimal degree of reactivity as measured by the galvanometer. On the other hand, patients with anxiety neurosis present a low skin resistance and a high reactivity. Dr. Fentress interpreted these facts by saying that in the former case a large portion of the total energy is bound, and that the patient consequently does not react strongly to psychic stimuli, whereas in the latter case the greater part of the total energy is free, with consequently a high reactivity. There is a question in my mind as to the propriety of the term bound energy. It appears to me that a patient with a compulsion symptom or a hysterical symptom has expended a large proportion of energy in the symptom, and that the energy is consequently not bound, but rather expended. According to this conception, the compulsion, the obsession or the hysterical symptom represents in a sense a solution of the patient's mental conflicts through which much of the total energy is drained off. The patient with an anxiety neurosis, on the other hand, has reached no such solution, and the energy, not being drained off, consequently exhibits a physiologic picture of sympathetic stimulation: sweating, dilatation of the pupils and similar features, with a consequent high reactivity as measured by the galvanometer. I confess that this, however, is only a minor objection as to terminology.

DR. A. B. YUDELSON: During 1922, at the Neuropsychiatric Division of the Federal Board for Vocational Education, it was our task to determine whether, in given cases, training was feasible and to determine the type of training indicated.

Much anxiety was shown by the patients, first, as to whether they would receive the compensation they needed during the training period and, second, as to whether they would be given the kind of training they preferred, so that after they had finished the course they could earn a livelihood. As the men were all anxious to train in the most lucrative and least laborious occupations, it was necessary to inquire into their previous educational equipment. Attempts were made to determine the truthfulness of patients under consideration, as it was noticed that the anxiety was accentuated during such inquiries. I recorded the blood pressure of patients presenting this anxiety. I found that when a question was relevant and the material was of primary interest to the patient, the rise was greater than if the question was less material or approached the indefinite. I found that even in the normal subject who was quiet and merely centering his attention on what was being done, when a question was asked the effort to give attention and make a response to the question produced a rise in blood pressure. When the question was not clear, the rise was higher. When cotton was placed in the external auditory meatuses and hearing was obtuse, so that effort was necessary to hear the question, a higher rise in the pressure was likewise produced.

My object in describing these findings is to answer this question: Should the first effort not be to study the normal person and see what the rise in blood pressure will be, first, when an indefinite question is propounded and, second, when a more difficult one is propounded, and then to figure from that level?

DR. CHARLES F. READ: I gained the impression that while proceeding with this work the essayists have closely considered the impressions of other psychiatrists and of themselves. The purpose evidently has been to contrive an objective method of procedure which will take the place of, or at least will assist in verifying, what have previously been subjective impressions. I wish to know to what degree they reached such conclusions as Dr. Solomon has presented without reference to psychiatric impressions of the subjects experimented with. Do they think that ultimately they will reach a goal where they can give objective findings that will be reliable in the diagnosis of states of free and bound anxiety and their combinations?

DR. CHESTER DARROW: There are many ways of recording the galvanic skin reflex. We have used several different methods and have arrived at a technic which we think has many advantages. We use a Wheatstone bridge circuit which has fixed resistances in three arms and which gives a balance when 300,000 ohms is introduced in the patient's arm of the bridge. With the use of a string galvanometer, additions or subtractions of 1,000 ohm steps give a scale for the later measurement of the patient's reactions. When the patient is introduced into the circuit, sufficient known resistance is placed in series with him to keep the total value near the balance of 300,000 ohms. His resistance at any time equals 300,000 ohms minus the resistance of the series, plus or minus the value of the deflection from the balance as measured by the scale of 1,000 ohm steps.

Much work has been done with the galvanic skin reflex in which the potential differences between two cutaneous areas have been the deciding factor. The recorded changes under such conditions are a function of the difference between the potentials at the two electrodes. This gives a rather complicated curve which is difficult to interpret, and we have found an advantage in the simplicity of the records obtained by using one indifferent electrode, with the skin pricked beneath, and one active (palm) or several active electrodes which may be switched in successively on different areas of the skin. The ambiguity that follows when reactions from two significantly different areas are combined in a single record, as when the two electrodes are attached to the intact skin of the palm and the back of the hand, or when finger electrodes are used, is thus avoided. Our electrodes are of constant area and of the nonpolarizable type made of zinc, zinc sulphate and kaolin, with the inclusion of a layer of absorbent cotton soaked in physiologic solution of sodium chloride next to the skin.

We use an appreciable external source of potential, giving in our circuit approximately 0.04 milliampere through the patient at all times, regardless of his level

of resistance. This further simplifies the record, because it reduces the changes to what are to all intents and purposes changes in resistance. They are really largely the result of counter-polarization in the tissues. At the present stage of the investigation, we think that this simplification of the curves has considerable advantages.

DR. ALFRED P. SOLOMON: We realize that in the short time available it was difficult to make clear subject matter that has taken us more than a year to understand. Dr. Favill's suggestion is of great interest, for the catatonic patient lends himself singularly to study with this apparatus. In one of our cases it appeared that there was a dissociation between motor activity, on the one hand, and psychic and autonomic activity, on the other, during the catatonic state, and that following the use of sodium amytal the dissociation disappeared. The point of disappearance of the catatonia could be more accurately determined with carbon dioxide.

Dr. Mackay suggested substitution of the term expended energy for bound energy. This gives me an opportunity to define more exactly what we mean by bound energy. We believe that energy is continually being expended in the binding mechanism, and that when binding is interfered with, the energy is expended in the production of anxiety. In other words, we regard the energy equilibrium seen in binding as a dynamic, rather than as a static, system. Clinically, when there is interference with the binding of energy by means of a system of compulsion or conversion, the result is the appearance of the liberated energy in a phobic attack or in other symptoms of anxiety.

Dr. Yudelson's interesting work on changes in blood pressure of recruits in the army is comparable to ours. We found that the increase in the blood pressure in response to crucial ideational questions is generally higher than that to indifferent ideational questions, and, further, that when the patient is irritated or antagonistic, the blood pressure rises even higher.

In answer to Dr. Read, I believe that ultimately such records will give objective criteria in terms of free and bound energy, which will be consistent with purely clinical observations. In the psychoneuroses the objective findings may well be of diagnostic value, but in the psychoses they show only those psychotic or psychoneurotic mechanisms present at the time of the test.

NEW YORK NEUROLOGICAL SOCIETY

Regular Meeting, April 4, 1933

HENRY ALSOP RILEY, M.D., *President, in the Chair*

A CLINICAL REPORT OF TREATMENT OF MOTHERS IN RELATION TO BEHAVIOR DISEASES IN THEIR FAMILIES. DR. LILLIAN MALCOVE (The Institute for Child Guidance).

The report is a representative clinical fragment of a larger unpublished study on the indirect treatment of psychiatric problems of the younger child. The procedure consists of a direct psychotherapeutic approach to the problems of the parent, especially the problems involved in a pathologic parent-child relationship. This type of treatment is to be distinguished from what is known as advice on the rearing of the child. In a brief introduction some general points are discussed; these points include the criteria for the selection of the parent rather than the child for treatment, the reasons for the choice of the maternal parent for the treatment and the modification in the technic of treatment necessitated by the fact that the mother originally came for treatment of the child and not of herself, and that the child as well as the mother has to be the therapeutic focus. The results of treatment show an equal symptomatic and general improvement in the mother and in the child. Actual emotional growth took place in both. The results in the

child depend on many factors, chief among which is the child's release from the mother's too involved relationship to him, and the better management subsequent to better understanding and better health in the mother. The major part of the report is a discussion of a case which, in addition to demonstrating the efficacy of this therapeutic research, illustrates the development of the maternal feelings and expressions from their earliest infantile origins. Each period of development is discussed so far as it contributed to the growth of maternal expression, starting with the first evidences noted in the play activities with dolls. The sum total of maternal responses as expressed later in the relationship to the child was in this way divided into its component parts. The influence of the mother's relationship to her child on the general development and on the formation of his problems is then brought out. By studying the maternal relationship one contributes to the general store of knowledge on maternal development. The mother is helped to modify her behavior in the interests of her child and of herself. This therapeutic method disposes of one of the most important factors relating to the problem of childhood.

THE EVALUATION OF PSYCHOLOGIC TEST RESULTS. MR. SIMON H. TULCHIN (The Institute for Child Guidance).

Psychologists recognize the difficulties involved in defining the precise nature of the functions measured by mental tests. Even in the field of intelligence tests, where much progress has been achieved, there still is lack of agreement not only on the nature of intelligence, but on the relative influence of native capacity and of training and experience on the test results. The problems of adequate test standardization are many, and the problems of test validation are even greater. Nevertheless, it is fair to state that tests have proved their value in clinical practice by making possible the measurement of capacities and limitations of the person studied and, in many cases, by offering valuable aid in the understanding of his difficulties in adjustment, as well as in the development of a plan of treatment.

This paper is concerned chiefly with the interpretation of results obtained from the most widely used of all intelligence tests, the Stanford-Binet examination, although many of the factors discussed are equally applicable to other tests. It is assumed that the examiner has ample technic in the performance of the test, discriminative judgment in test selection and in variation of routine procedure, ability to secure good cooperation, which includes awareness of the subject's attitude toward the examination, and the ability to recognize whether or not the rating secured is to be considered reliable. The factors which must be considered in the adequate interpretation of test results are grouped into four divisions: (1) factors influencing test performance; (2) limitations of the test; (3) correlation with other tests, and (4) criteria other than test results.

1. In this group are considered the subject's physical condition, the language spoken at home, the race and nativity, the social and economic status and the special abilities and disabilities. The need for recognizing minor deviations such as slight visual or auditory defects, fatigability and unusual slowness of response is stressed because of the possible influence of the deviations on the test results. The child who comes from a home in which a foreign language is spoken may be handicapped on a verbal test of intelligence. The differences in intelligence shown by children of different racial and nationality groups may be a result of cultural and social factors which need careful evaluation. The differences in the rating of intelligence shown by subjects of different social and economic status need to be interpreted. The test results are affected when a child shows some unusual abilities or when he is handicapped by a specific disability.

2. In this division are considered the chronological age of the person tested, the problems of adult mental age, the special advantages or disadvantages of training and the qualitative differences noted for some of the tests. The highest mental age which can be obtained on the Stanford-Binet examination by passing all of the tests is 19 years and 6 months. The older the child, the smaller becomes the range

of tests which he may be given and the more limited the possibilities of registering high intelligence quotients. Taking 16 years as the upper age limit for calculating intelligence quotients, the highest intelligence quotient that can be obtained by persons aged 16 years and over is 122. Attention is called to the fact that frequently an older sibling is compared unfavorably with a younger brother because of a lower intelligence quotient, although both children may be equally bright by all other criteria. The examiner should consider the possible influence of special advantages or disadvantages on test results. Comparisons of test responses of feebleminded adults and of superior children having equivalent mental ages have shown that the defective adult is more likely to succeed in tests requiring information and life experience, while the bright youngster earns his mental age score more on tests relatively free from the influence of direct experience. Analysis of test results in the light of these findings is frequently helpful, especially for children whose school experience is limited.

3. In this group are considered the results obtained from performance tests and educational tests. Both are valuable as a check on the results obtained from the Stanford-Binet examination. A high correlation gives the examiner confidence in his results, while wide discrepancy calls attention to the need for an explanation. Further study may be indicated.

4. In this division are considered criteria other than test results, such as are offered by the developmental history, the school history and estimates of intelligence which may be obtained from several sources.

The social examination contains a detailed summary of the developmental factors. The age of teething, sitting, walking, talking and other accomplishments is to be considered in relation to test findings. The school history, in telling of the child's progress through the various grades, offers much help in forming an estimate of the child's intelligence. Estimates of intelligence may be obtained from teachers as well as from the workers in the clinic who have contact with the child.

If properly administered and interpreted, psychologic tests offer much help in clinical practice. When improperly administered and taken at their face value, with little or no correlation with other available data, they may serve as a dangerous weapon.

A Study of the Sucking Reflex of Dogs. Dr. D. M. Levy (The Institute for Child Guidance).

Of six dogs in a litter, four were taken on the tenth day of life and fed by bottles. The quantity of milk was controlled so that all dogs maintained approximately the same weight. During the experimental period of twenty days, an attempt was made to keep all conditions constant except the sucking time at feeding. One pair of dogs, called the long-time feeders, sucked from bottles with small-holed nipples, and after feeding were given supplementary sucking on the examiner's finger. They averaged about eighty minutes daily of sucking at meals. The other pair, called the short-time feeders, sucked very rapidly from bottles having large-holed nipples, averaging thirteen minutes daily of sucking time at meals. The short-time feeders exclusively developed sucking movements for several minutes after meals, sucking noises during sleep, sucking of their own bodies and sucking or licking of objects in the kennel. As compared with the other pair, the short-time feeders sucked the inserted finger of the examiner in various tests throughout the experimental period more vigorously and more frequently. The instances in which the long-time feeders sucked the inserted finger occurred from one to four hours after meals. The latter pair never sucked during tests performed immediately to within forty minutes of the feeding time.

In more than thirty observations in which each pair was given access to each other, sucking on the body of one dog by the other occurred in each instance in the case of the short-time feeders, and in seven instances in the case of the long-time feeders. In the latter, the seven instances occurred just before feeding time. Various tests of licking the examiner's palm showed similar contrasts.

Observations made when all six dogs were again brought together on the thirtieth day, until the sixty-fourth day of life, revealed increased licking activity after feeding on the part of the short-time feeders. During the period in which the long-time feeders were allowed to suck to the point of satiety, there was apparent a progressive diminution in the time necessary to reach this point.

In order to maintain the weights of the artificially fed dogs at nearly the same level, it was necessary to feed the short-time feeders about 7 per cent more than the others. This necessity was attributed to the observed greater motor restlessness and lessened time in sleep of the short-time feeders.

An "accessory" movement (a rhythmic motion of the forepaw of dog 2, with ensuing sucking activity as described, occurred on the tests made on the week-end observations on the thirty-first, thirty-eighth and thirty-ninth days of life), produced by rhythmically moving the forepaw of one of the dogs while feeding, was utilized successfully as a means of initiating sucking movements in the third and fourth weeks of life only. An "accessory" posture, attempted with one of the dogs, failed to initiate sucking movements.

Dogs fed on the breast were consistently much heavier than the long-time feeders, and the latter were heavier than the short-time feeders. As compared with the others (after the experimental period of twenty days), the short-time feeders remained more apart from the group and had difficulties due to slowness in gulping food.

Conditions that prevented completion of the sucking phase in the feeding act, i. e., conditions that caused an insufficiency of sucking, produced in the animals studied excessive sucking and licking activities. These findings in dogs confirm similar observations in the study of finger-sucking in infants, and of sucking habits in the calves of dairy cows.

In dogs allowed to suck to satiety, excessive sucking, though less vigorous or persistent, occurred from two to four hours after the latest meal. This sucking excess was attributed to hunger, a second factor in the genesis of sucking habits. The observation may help to explain the high frequency of finger-sucking in infants on a four hour feeding schedule in which both factors, sucking deficiency and hunger, are combined.

Innate difference in sucking time was observed in the long-time feeders. The difference amounted to an average of six minutes per day for the period of the experiment. If the observations made on feeding apply to human infants, innate differences in sucking are too small to affect the large majority of finger-suckers, since the difference in actual sucking time and optimal time (i. e., to the point of satiety) is much greater in such cases than the small innate difference.

"Accessory" movements during feeding, analogous to accessory movements during infantile finger-sucking, may be produced experimentally.

Observations suggestive of the influence of excessive sucking activities on nutrition, motor energy and general personality of the short-time feeders demonstrate interesting possibilities of research in that direction—an experimental approach to the problems of the erotogenic zone as elaborated by Freud in his "Three Contributions to the Theory of Sex."

THE SIGNIFICANCE OF CERTAIN BODY MEASUREMENTS. DR. ROWLAND G. FREEMAN, JR. (The Institute for Child Guidance).

The paper describes changes in the relationship of chest width and hip width during the course of development, showing that from birth to 4 years of age the chest exceeds the hip in width, but that thereafter the width of the hip exceeds that of the chest, the difference between the two measures being greater in the female than in the male. The female hip width becomes greater than that of the male at about 7 years; there is a second period of accelerated growth of the female hip width between 9 and 10 years, and a third at puberty. After puberty there is an acceleration of growth in the male chest width not shown in the female. The index used to describe these changing relationships was calculated by dividing

the chest width by the hip width. Values for this index exceed 100 up to the fourth year in both males and females and diminish to 93 at the age of puberty in the male and to 85 in the female. Lower than average indexes for a given age were regarded as a sign of accelerated sexual maturity because of their high correlation with an early onset of menstruation in girls. Higher than average indexes for a given age were regarded as a sign of retardation because of their high correlation with retardation of genital development in males. A group of patients with the Fröhlich syndrome showed high indexes. The conclusion was drawn that body build in this syndrome is not feminine but infantile. The frequency distribution of the index of chest width to hip width of 100 children seen at the Institute for Child Guidance was bimodal. Children in whom a lack of energy was one of the complaints tended to have high indexes. The children who numbered among their difficulties restlessness, hyperirritability and fatigability tended to have low indexes. Changes in the reciprocal activities of the maturity factor of the anterior pituitary gland and of the gonads were suggested as the cause of the variation in the index of chest width to hip width and in the production of energy. Two patients with Fröhlich's syndrome were treated with 30 cc. of antuitrin S, with a marked increase in overt activity and subjective feelings of desire to do more, but no change in the basal metabolic rate or in the rate of growth.

A Preliminary Report on the Processes of Treatment and the Results at the Institute for Child Guidance. Dr. Lawson G. Lowrey.

Beginning in the fall of 1930, an elaborate study of the processes of treatment and the results has been carried on with the assistance of a group of students from the Smith College School for Social Work. More than 450 patients who had been treated and with whom the contact was closed were available for this study. Of these, 131 were classed as satisfactorily adjusted at the time of closing, 255 as partially adjusted and 100 as unimproved. Analyses were made of all factors that could be submitted to statistical manipulation. Follow-up visits were made to the family and, when there was no contraindication, to the school, to see what developments there had been following the cessation of contact with the institute. The new material was then revalued by the staff, and a new status assigned if that seemed justifiable.

In general terms, the study indicates that none of the factors which may be statistically studied are of particular importance with reference to the outcome of the case, especially when one contrasts the patients classed as satisfactorily adjusted with those classed as unimproved. There was slightly greater success with the older group than with the younger group of patients. The factors involved are complex and are to some extent related to the differences in parental problems and parental manipulation of the children. Over a five year period there was some shift in the type of problems. Problems in socially unacceptable behavior showed a marked decrease in number, while problems in personality reactions and in habit formation showed a marked increase. An important by-product of the study is the development of a thorough type of closing analysis of the processes utilized in treatment and of the results achieved, with reference not only to the original problems of the child but to the situation as a whole.

DISCUSSION

Dr. Louis Casamajor: Dr. Malcove and Dr. Lowrey stressed one important factor: the necessity for the treatment of the mother. Many of us have long thought that the only etiologic factor in a nervous child was a mother incapable of bringing up a child. The case reported by Dr. Malcove was extremely instructive; there is need of more of that type of case study in the literature, if one is to convince the public of the need for child guidance. It must be shown to have value. As long as people look on the question of child guidance as though the child were the only person at fault, I think there is little hope for society in the future.

Mr. Tulchin's study of the work on intelligence tests is of interest. He stressed the limitations of testing mental ability, and such stress, I think, is much needed. Dr. Potter emphasized the same thing in a recent talk before the combined meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, and the New York Neurological Society. He brought out many of the points mentioned by Mr. Tulchin concerning the limitations in technic and, more especially, the limitations of the test itself. Mr. Tulchin has placed before us seriously the extreme limitations of the intelligence quotient—the variations in the possibilities of the intelligence quotient, the greater opportunity for a high intelligence quotient among the young as compared with the older age groups, which is caused by the fact that all mental tests have the age of 15 as their limit. Above 15 years and in the lower years there are great inaccuracies. The use of mental tests has been possible in school children, because the school child is in a standardized environment. Children of a certain age learn the same things, no matter where they are; when one has standardization of the environment, one can draw some conclusions concerning the results of the reactions of that standardized environment on an individual person. Beyond 15 years, when the children leave the primary schools, the environment is no longer standardized. Some go to work as laborers; some go to high school; some go to college, and others enter professions. There is no standardization from that point on, so that one cannot speak comparatively of mental tests beyond that point, as Mr. Tulchin has said. One wonders whether the tests are tests of intelligence at all. Mental tests only reflect the utilization of the environment. Perhaps that is what intelligence is, but that is not all, because I think we all agree that the evaluation of the utilization of the environment does not reflect the sum total of intelligence. That point was well stressed by Mr. Tulchin in his remarks about the feebleminded adults and advanced children. The differences in the type of intelligence were shown. The one shows more skill in learned things; the other shows the highest skill in practical things.

I have been interested in the application of mental tests to medical students. At the College of Physicians and Surgeons we have the problem of selecting the medical students for the first year class from among seven to ten times as many students as can be accepted. We have tried to find a method of determining which applicants to take. We do not wish to use examinations, which are only a form of intelligence test, and the ability to pass examinations has little to do with intrinsic ability. For the same reason we do not wish to use college grades. We have interviews with the students. We have no standardized questions, except six or eight which are used to start the conversation. These are about matters of fact for statistical purposes. We have been doing this for two years. It will be interesting to see how the ones picked by the committee rank at the end of the second year. Perhaps in ten or fifteen years we may find out something about our mistakes. We are groping in the dark.

What struck me as of greatest interest in Dr. Levy's report was that the length of sucking time was of greater importance than the amount of food. If the sucking time was shortened, the amount of food had to be increased in order that the body weight might be kept up. Apparently there are two kinds of hunger; there is the tissue hunger—the need of the tissues for new material to build the rapidly growing organism—which is reflected in gastric hunger, by discomfort and probably by pain, but beside this organic hunger there is apparently also a sucking hunger. Just what this means I do not know. Dr. Levy spoke of it as a secondary factor. I rather doubt that it is secondary. I think that it is probably a factor as important as the other. It is a libidinous need, a need for satisfaction at a very low psychologic level, and it is to gratify that need that the animal gratifies the other, possibly greater, organic need—the tissue and gastric hunger. What do these two kinds of hunger have to do with the make-up of the person? Is the possibility of a coordination of the satisfactions between these two hungers the best situation, both psychologically and organically, for development from infancy into childhood, from childhood to preadolescence, and from adolescence to manhood? Thumb-sucking may be a regressive phenomenon in which that very simple sucking hunger

persists in children as one of the factors which the child fixes on in order to maintain its infantile status.

One point that interested me particularly in Dr. Freeman's paper is that the status of the Fröhlich syndrome is not feminine, as has been claimed, but infantile. That must be true. In the case of a developmental anomaly, I do not see why one should consider the status as feminine.

Dr. Lowrey stressed again the point that Dr. Malcove brought out: the need for treating the mother. Dr. Lowrey has made an admission tonight, which confirmed a suspicion that all of us have had: That the name "The Institute for Child Guidance" is an absolute misnomer. It is not an institute of *child* guidance at all, it is an institute for parent guidance. The suggestion that the proper place for the treatment of the child is in the school is likewise the result of considerable experience. The psychiatrist is not going to do the work alone. Nor does the psychiatrist have any opportunity of making the child such as the parents want it to be. One would have a much better outlook for the future if one could make the parents such as the child wants them to be. The treatment of the child is the process of socialization of the child. If Dr. Lowrey has done no more and can do no more in The Institute for Child Guidance than to prove that child guidance means the socialization of the child, and if he will prove that the principal stumbling block in the way of the socialization of the child is the parents, I think that he will do a great deal for civilization. He is talking now about his follow-up reports. We have all been waiting anxiously for them. He will soon have to give an account of the talents which were given to him. In a few years we shall see the results of all of his work. We shall find out by actual experience what we have only guessed at in the past: whether this idea of child guidance is good or not. I am waiting and looking forward more or less impatiently for those results to appear.

Dr. Henry H. Hart: Dr. Malcove did not give details as to the number of appointments or the number of hours spent, nor as to the particular kind of technic that she used, whether it was of psychoanalytic or of a modified psychoanalytic type; neither did she say how deep a transference was necessary in order to obtain this material. We see so many cases of this type in our clinics; the practical question arises as to how we can treat patients so intensively. Scarcely a week goes by that we do not find some deep incestuous attachment which at first seems hopeless to treat. In a case of this sort no doubt there were certain factors that made the psychiatrist feel that the case was hopeful, and that considerable effort might result in success. I think it might be of interest to hear from Dr. Malcove on that point. In these cases we so often hear of the absence of the father. The father seems to be a nonentity. Over and over again the clinical records disclose the absent or the passive father, and one wonders why this is so, and what part that plays in the causation of these problems. Is the father a nonentity because the wife selects such a partner on account of her own dynamic problems, or is it because of the economic necessity of the father's absence? Are we going to see this type more and more, or, with the increase of leisure, is the father going to play a greater rôle in the handling of the child?

Mr. Tulchin's paper seems to bring out the point that everything depends on the psychologist as a personality, on his training and understanding of human nature and not on the tests themselves. It seems to bring us to the rather humble conclusion that the tests are very fallible, that the imponderable factors of human nature are still imponderable and that they are still the most dynamic and important factors. For that reason, it seems to me, we have a long way to go before psychiatry can be called a science.

Concerning Dr. Freeman's paper, I have looked up some of the recent literature on anthropometric studies in children, and the one paper which seemed closest to Dr. Freeman's, namely, that of Lucas and Pryor (Physical Measurements and Physiologic Processes in Young Children: Some Correlations, *Tr. Sect. Dis. Child., A. M. A.*, 1931, p. 166) presented results similar to those of Dr. Freeman, but he

used a different index. I understand that there are 63 different indexes one may use in the study of children. Kretschmer found women hard enough to classify; he never attempted to classify children. He found that there was quite a variability in typing women, and apparently this difficulty has been found in other cases. One finding of Lucas and Pryor in the examination of 110 children was that the children with anorexia showed a low index. The index they used was a body width-length index, the width divided by the length, multiplied by 100. Whether there can be any correlation between these two indexes I do not know, but they found that children with a low index, in which the length exceeded the width, the so-called linear type, showed marked anorexia. They also found a considerable increase in the basal metabolic rate. Apparently Dr. Freeman did not find any variation in the basal metabolic rate. There seemed to be some definite correlation in the findings of Lucas and Pryor, as the linear type had a rather high basal metabolic rate and the lateral type a rather low rate.

The paper of Dr. Levy dealt with a problem which has been a common and poorly understood one: the question of the sucking activity in children, and the light that the observations on dogs throws on it. Certain questions arise in connection with this: The first is what type of milk formula did Dr. Levy use? He did not state, and one wonders whether there might not be some connection with the differences in growth and weight in the dogs. One wonders whether work with other mammals will corroborate this type of study, and whether observations on dogs that are breast-fed with regard to the duration of feeding time would give any interesting comparisons. I think, too, that this paper and the type of experiment could perhaps be carried on in respect to the ultimate psychologic effects of the protracted absence of feeding or sucking activity on the personality of dogs. Dogs have personality, and I think that it might be of interest to make some such study. I wish to ask Dr. Levy how he explains the fact that in some infants thumb-sucking occurs at the time the infant is being fed at the breast. The particular infant I am thinking of was fed on a four hour schedule.

I think that we are much in danger of exaggerating tests and mechanical means of examining people. Today I happened to see a monograph with an elaborate scheme for measuring inferiority feelings. The scale was marked in 100 degrees; the degree of inferiority feeling could be estimated by whether one answered "yes," "no" or "doubtful" in situations in which the feeling of inferiority developed. This is illustrative of a great many approaches to human problems, and is one reason why we go through periods of disillusionment and are apt to give up the problem of studying man from an objective point of view. It seems to me that a great deal can be obtained from psychologic tests, especially in respect to vocational tests, for we have heard much about advising youths and adolescents as to what their capacities are. I do not know whether Mr. Tulchin can reassure us as to the validity of such tests at the present time, but it seems to me that much can be done with the recognition of the personal factor.

DR. BELA MITTELMANN: There have been innumerable attempts to utilize anthropologic measurements for psychopathologic work. So far, I believe, only those of Kretschmer have proved of any practical value. It is obvious that Dr. Freeman attempted to find an index that in a sense would be an index of endocrine activity. All such single indexes are of questionable value. In different endocrine disorders, different anthropologic measurements are found to deviate from the "normal." In Fröhlich's syndrome the shoulders are very narrow as compared with the hips, whereas the relation of height to the span of the outstretched arms as well as the relation of the distance from the symphysis pubis to the vertex of the head to the distance from the symphysis pubis to the soles of the feet is usually found to be normal. The measurement from the symphysis pubis to the soles of the feet in infants is much smaller than is the measurement from the symphysis pubis to the vertex of the head. This is found to be the case in true infantilism. In eunuchoidism, the opposite relationship exists. In other words, one cannot say that the measurements in Fröhlich's syndrome are uniformly infantile

or even pathologic. A single index seems to give a distorted picture. It will be interesting to see whether the single index suggested by Dr. Freeman proves of special value in a large series of unselected patients with behavior disorders. Of course, Dr. Freeman emphasized the limitation involved in the number of cases he has examined.

I had some experience with the use of the hormone occurring in the urine of pregnant women in Fröhlich's syndrome. Depending on the dose, one can obtain a definite genital development. One cubic centimeter daily seems to be the optimum dose.

In Fröhlich's syndrome one finds two types of behavior disorder that seem to be more or less characteristic. One type of patient, as Dr. Freeman pointed out, is extremely inactive. I think that another type shows hypermotility and destructiveness practically from birth. Later, this type may show pathologic liars and thieves. "Hypomotility and hypermotility" are, perhaps, not the best terms to use. A patient may not engage in active sports; that is, his actual energy output during the day may be comparatively small, and yet the behavior disorder may be that of constant restlessness, unmanageability and destructiveness. These are the children whose attention cannot be held during the interview, and who run all over the room, or pick up one object after another. This does not seem to be a psychogenic compensatory process, but rather a primary organic one.

DR. GEORGE VAN NESS DEARBORN: Every one interprets these matters of medical psychology differently, and my interpretation of Mr. Tulchin's paper was that he did *not* stress the limitations of tests, as Dr. Casamajor implies; indeed, he distinctly said that "they proved their value." I have given at least 4,500 elaborate psychologic tests in the last eleven years, and I can assure you that the work has been of much value in diagnosis, especially in picking out cases of mental deterioration. In about 20 per cent of these psychologic examinations we did not use the Binet-Terman test, but a performance test, usually the shorter Pintner-Paterson set; this has two or three tests for abstract intelligence. It is mostly a mechanical test of various forms of behavior and of performance which have been standardized accurately.

The matter of qualitative analysis in the Binet-Terman test suggested by Mr. Tulchin interests me; I am sure that we are only at the beginning of rather important studies in the qualitative aspect of test results. For an example of their importance in these examinations of the feebleminded or psychotic person, I wish to suggest a single group of tests, namely, the five in the Binet scale which inquire into the matter of similarity and dissimilarity. That is a fundamental mental principle—the differences and the similarity between things—and those tests which require an answer as to similarity and dissimilarity are of great importance in picking out the feebleminded person as contrasted with the deteriorated one. That is an example of the use of the qualitative study which Mr. Tulchin said was about to begin.

I wish to say to Dr. Casamajor that I am sure that the College of Physicians and Surgeons is on the right road in picking members of the freshman class by asking them sundry questions, and in having a common-sense and sociomoral contact with them. Nobody would ever dream that the Binet-Simon or any other scale would measure a person's potentiality of being a good physician. But there are many really useful personality tests and standards being developed, which do measure the affect in an elementary and imperfect way; these are beginning to give us a means of estimating personality.

Tests are as applicable to adults as they are to children. The intelligence quotients range up to 123, and the large majority of adults are below that very superior intelligence.

DR. LILLIAN MALCOVE: In replying to Dr. Hart's three questions, I shall start with the last. It is a comment with some wonderment on the frequency with which the fathers of problem children are ineffectual and passive. This is true only to a certain extent, as the treatment often shows that, given the

opportunity, they could play a more active rôle. The second question is a pertinent one. The features in the situation that were regarded as hopeful were considered from three points of view: the child, the mother and the experience of the therapeutist. The child was not a severely neurotic one; he was what we call a "behavior problem." The mother had been ill, but was seen at the time of a free interval. Furthermore, she was intelligent and cooperative, and had considerable understanding of her part in the child's problems. In regard to the third question, the technic, this would take too long to describe. The subject is discussed in some detail as a part of a project not yet published. I shall answer the one point as to whether it was a modified psychoanalysis. It was intensive psychotherapy, to which some psychoanalytic knowledge was applied. One would have to know the practice of psychoanalysis to apply a modified form of it.

MR. SIMON H. TULCHIN: The question whether we really measure intelligence with these tests is extremely important. I believe that we do, and there is some empirical evidence to show that we do. I am much interested in the experiment of the medical school in the selection of students which Dr. Casamajor described. I hope that the school will admit a control group of students who do not meet all of the requirements set up by the committee, so that a follow-up study of such a group will be possible.

I agree with Dr. Hart that there is no simple path to the understanding of human nature and that a great deal more than an intelligence quotient is necessary.

In response to Dr. Dearborn, I may say that the limitations of the tests were stressed in order to enhance their value. I agree with him that they have a decided value in both children and adults. It is easy to give mental tests, and this point was stressed so much by psychologists that "six-week testers" became quite the vogue. Because the work of the psychologist lends itself to numerical expression and because such expression has a certain air of finality about it, the fact is not less important that the psychologist considers and evaluates his results in the light of all the available data noted in the clinical study.

DR. ROWLAND G. FREEMAN: In regard to Dr. Hart's question on Lucas and Pryor's work, it is true that the nonenergetic children tend to be somewhat shorter in comparison to their breadth than other children, and that the energetic children tend to be more linear. For a while I used an index of shoulder width and height, but I found that it correlated much less highly than the index for chest width to hip width. As to the question why the index was chosen, it was first chosen because in drawing growth curves and comparing different parts of the body in their growth, chest width and hip width were the only measures that showed a changing relationship during development. All other measures varied directly with each other. The chest width-hip width was the only relationship which did not correlate highly with other single measures.

As to hypermotility, I have never seen any hypermotility in children with the Fröhlich syndrome. We see a great many who are hyperirritable, but it is usually a compensatory motility on the basis of a laziness which prevents them from taking part in the normal activities of children. We see a great number of children who come with the complaint that they are aggressive and given to fighting, and when we analyze the situation, we find that all is done in a protected situation and not in a group.

As to the children with the Fröhlich syndrome, it is true that the shoulder width can be narrow or broad; the high index of chest width to hip width, however, seems to be a constant finding.

DR. D. M. LEVY: The remarks on Fröhlich's syndrome are of special interest to me since I have been studying the problem in thirty patients with such a syndrome. I do not think that the group can be characterized by any one of the descriptions given: that the patients are pathologic liars, thieves or all hyperkinetic. They seemed to show variable problems running through the usual range of difficulties, as we see them at the institute. So far, one characteristic of the group appears significant, namely, that their problems are related to the submissive type of difficulties.

In regard to Dr. Lowrey's statement about differences in therapeutic findings in older children, I wish to offer this suggestion: The set-up of the Institute has been adapted to the adolescent rather than to the young child. It may not be true necessarily that the problems are deeper in one group than in another, but rather that our personnel of Fellows in Psychiatry are better equipped to treat the young adolescent. Furthermore, the problems of the older child respond to direct therapy more readily than do the problems in the younger group in whom the parent-child relationship is so significant. Moreover, it is only in recent years that treatment of the parent at the Institute has become more intensive.

In reply to Dr. Casamajor's question about sucking hunger, and to his statement in regard to it as a secondary phenomenon, may I say that three factors must be present: (1) deficiency in sucking time, (2) hunger and (3) inherited or innate differences. The innate difference in sucking time in the animals studied appeared insignificant. In children previously studied there was no relationship between finger-sucking and nutrition, either as to body weight or to, for example, the presence of rickets. Children with severe rickets show a response to sucking time similar to that of normal children, and they do not appear to have finger-sucking habits more frequently.

In reply to Dr. Hart's question, I do not think that the food I gave explains the differences in weight of the artificially fed animals, since they all received the same formula. The formula used was a dried lactose powder mixed with varying proportions of water, depending on the age of the animal, the formula being changed weekly. Sucking of the breast-fed dogs was not timed. I think it is safe to assume that they did much more sucking than the animals who were on a three hour schedule of six feedings daily, since they could suck at any time, especially in the early weeks of life.

The influence on the personality of the animals is merely suggested. However, one of the short-time feeders, as compared with the others, became distinctly antisocial, never joining the others and usually hiding somewhere. Both short-time feeders are now eating-problems. One must be fed separately; the other, while eating, snaps at the pups who dare eat from the same dish. In both cases the difficulty is due to their slowness in gulping down food.

An attempt has been made to use the same method in white rats. It failed because the rats would not feed artificially.

DR. LAWSON G. LOWREY: In answer to Dr. Casamajor that the process is not child guidance but parent guidance, I should prefer to have it called situation or family guidance, because it is all that this implies. However, we emphasize the child because one is thinking of the child as an individual who has yet to grow up and meet all of the difficulties to which it must adapt itself as an adult.

I should be sorry if I gave the impression that we did not also treat children intensively by psychotherapeutic methods. I have tried to make it clear that we treat not only the child but also the parents, or, to put it differently, not only the parents and the situation, but also the child. I did not mention that there has been a gradual shift in the major types of problems coming to us. In the first year the problems of socially unacceptable behavior comprised 57 per cent of the group, while in the fifth year they included only 40 per cent. Problems in personality reactions comprised 30 per cent in the first year, and 39 per cent in the fifth year. In other words, during the past year we have had more children classified as neurotic. During the past year we have been experimenting by changing our general system of appointments from an average of once a week to three or five times a week for a smaller number of weeks.

We have under way this year a publication program which we hope to complete by the end of June, which will involve publication of one book on the processes of treatment and results; another from our research unit, of which Dr. Malcove spoke, on certain aspects of problems in treatment, particularly with reference to various approaches to the intensive treatment of mothers, and a series of edited and annotated case studies which we hope may be useful for teaching purposes.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Secretary*

Regular Meeting, April 20, 1933

E. S. ABBOT, M.D., *Presiding*

A CASE OF ACUTE POLIOMYELITIS. DR. LAURENCE D. TREVETT (by invitation) and DR. JAMES B. AYER.

This article will be published in full in a later issue of the ARCHIVES.

THE RELATIONSHIP OF THE CEREBROSPINAL FLUID PRESSURE TO THE SYSTEMIC BLOOD PRESSURE. DR. FRANK FREMONT-SMITH and DR. H. HOUSTON MERRITT.

This article will be published in full in a later issue of the ARCHIVES.

STUDIES IN READING DIFFICULTIES. DR. DONALD D. DURRELL.

Of 635 children with normal intelligence but with marked difficulty in learning to read, a large number appeared to have no sensory or physiologic irregularities. An analysis of the difficulties showed many confusions, inadequacies of association and faulty habits. Inadequate equipment for beginning to read was shown by mental immaturity, poor vocabularies, inability to discriminate between letter and word forms, faulty concept of the reading task and low motivation. Certain common faults appeared in establishing quick recognition of words: confusions due to recall of words through partial cues, absence of association between letters and sounds, difficulties in synthesis of sounds, meager word meaning associations, loss of meaning through overanalysis and lack of attentive practice in mastering of words. In the more complex reading processes, difficulties appeared in integration of words into thought units, in adaptability of reading rate, in richness of intellectual or imaginative associations while reading and in comprehension of complex sentence structure. When corrective procedures were given, rapid gains were made. An individual test survey of 1,130 children in the middle grades showed 4 per cent to have severe difficulties in reading. Boys had more difficulties than girls, the ratio being 2 to 1. Difficulties in reading affect the scores of intelligence tests very unfavorably, some being lowered as much as 40 points in rating of the intelligence quotient.

DISCUSSION

DR. S. COBB: I have had little experience with difficulties in reading. Dr. Durrell's work is original and convincing. I think that in the last years the importance of left-handedness and right-handedness has been overemphasized.

DR. W. F. ROTH: Dr. Durrell's statement regarding the finding of poor motor coordination in so many of his nonreaders is of great interest. In most of the small number of nonreaders I have studied, a certain lack of coordination is striking. This suggests the possibility that reading disability is but one result of a partial but rather general disorganization of the central processes. Perhaps this is the basis of the ocular incoordination about which one hears so much.

DR. D. GREGG: Apropos of the more common occurrence of stuttering among boys than among girls, can you say whether the words over which people stutter commonly possess or lack motor content?

DR. D. DURRELL: That is probably a significant factor. In beginning to read the boy often finds the words overchildish. Later, the subject matter is primarily literary and historical. Girls make greater gains in such work because they conform to the teaching and the motivation of the classroom. At all stages

of reading after the first six months, girls are definitely superior to boys. We find in remedial work that if we select words and subjects that appeal to boys as useful and sensible, the words are learned more readily and are retained longer.

DR. D. GREGG: It was my experience when teaching physics that the boys were quicker to grasp certain problems than the girls. For example, a boy knew from personal experience that the higher a ball was thrown, the faster it dropped on falling, and from this he could grasp the physical law of falling bodies more readily. On the other hand, there are many words without motor content, words the meaning of which cannot be acted out or experienced, and in these words girls might well have less difficulty than boys. Predominance of color blindness has been noted among boys, and this, I believe, is attributable to the fact that girls have more experience in distinguishing and picking colors. If all words had the same degree of motor content, perhaps boys would not be handicapped in learning their meaning, because of the boys' predominant motor experience. Dr. Orton quotes as examples "was" and "saw," "dog" and "god." Are there reversible words with meanings that are not quite so diverse?

DR. D. DURRELL: Yes. The reversal error ordinarily appears in all beginners at reading. Its occurrence is probably due to incomplete analysis of perceptual cues. This explanation more nearly agrees with the observed facts than Dr. Orton's more elaborate theory.

DR. O. RAEDER: I knew a boy, aged 6, who could not learn to read in the first grade. His father was well thought of by the school master, and the school authorities thought that the boy should be promoted; he was placed in grade 2 and intensively tutored in reading. At the end of the second year he was still nearly as bad. In the third grade he began to learn. He was promoted from the third into the second division and in the middle of the third year had become an average third grade reader. Reading ability apparently develops at various ages in different children, perhaps earlier in girls. Arithmetic is much easier for boys, and reading is easier for girls. In this case the boy finally learned to read and, what is equally important, began to enjoy reading. Perhaps he should have been kept out of school two or three years longer instead of being intensively trained before he was ready; thereby the danger of causing emotional disturbances might have been avoided.

DR. C. A. MCDONALD: It seems to me that you have presented defects in teaching rather than defects in reading.

DR. D. DURRELL: There has been much unnecessary mystery about "non-readers." From my experience I should say that any child with a mental age above 6, good sensory equipment and no physical handicaps to affect his attention can learn to read. The cases presented were those in which no physical difficulty was found. The difficulties appear to arise from faults in the process of learning. Our method is to take an inventory of faulty habits and confusions in the various fundamental elements in reading, and from this inventory to plan a systematic procedure for remedial work. Many difficulties in reading rest on sensory defects, and no child should be tutored in reading until a careful examination has been made.

INDEX TO VOLUME 30

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

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News and Comment

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CONTENTS